NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy [ID663]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy [ID663]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Panobinostat for treating multiple myeloma in people who have received at least 1 prior therapy

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies. **Also as a result of the timing of the approval of the Patient Access Scheme submitted by the company, this premeeting briefing does not include the ERG's critique of the PAS submission template – this will be provided in a separate document.**

Key issues for consideration

Clinical effectiveness

Generalisability

- The clinical data from the company is based mainly around the PANORAMA-1 trial and those who have had an immunmodulatory drug and bortezomib along with at least 2 previous treatments, which is the population in the positive CHMP opinion. This population represented 19% of the PANORAMA-1 trial sample. Is the population in the trial generalisable to the UK?

- The median age of patients in the PANORAMA-1 trial was 63 years. In the UK 60% of patients are diagnosed at 70 years or older.
- Patients in the PANORAMA-1 trial who had received previous stem cell therapy were higher (56% and 59%) than patients in the UK (18%).
- The frequency of bortezomib administration was different to that recommended in Technology appraisal 129 (TA129) and in the UK where bortezomib treatment would stop at cycle 8.
- In PANORAMA-1, bortezomib was administered intravenously. Guidelines in the UK still suggest the use of intravenous bortezomib; however, according to the clinical expert advising the ERG, in UK clinical practice bortezomib is being administered subcutaneously.

Relevant comparators

- In people with refractory or relapsed multiple myeloma, who have received at least 2 previous treatments (the population in the positive CHMP opinion) only a comparison with lenalidomide and dexamethasone has been carried out. The PANORAMA-1 trial had bortezomib plus dexamethasone as the comparator. What is the most relevant comparator?

Indirect comparison

- Four different indirect treatment comparison methods were tested (common comparators method, naïve comparison, unadjusted cox and matching adjusted indirect treatment comparison) for the subgroup of patients who had received at least 2 previous treatments. Are the results from the indirect comparison comparing panobinostat plus bortezomib and dexamethasone with lenalidomide and dexamethasone valid?
  - The Unadjusted Cox method was chosen to estimate the relative effectiveness between panobinostat plus bortezomib and dexamethasone and lenalidomide plus dexamethasone for the subgroup of patients who had received at least 2 previous treatments, however this method generated Kaplan-Meier curves that do not satisfy the key assumption of proportional hazards.

- The ERG considered that all these analyses of indirect treatment comparison were likely to be invalid.

Cost-effectiveness

Cost of panobinostat

- Although the PANORAMA-1 trial protocol detailed that patients were to be treated for a period up to 48 weeks with panobinostat, some patients had a treatment duration of greater than that. To capture the efficacy related costs the company did not censor these patients in the model. However, the proportions of patients continuing beyond cycle 20 are very low. Therefore patients keep accruing costs and QALYs associated with the treatment beyond treatment duration (as per the marketing authorisation). Are the costs in the company's model overestimated for panobinostat?

Parametric curve fitting of trial data

- The company used parametric curve fitting of the PANORAMA-1 trial data in its base case for the subpopulation who had receive at least 2 previous treatments including an immunomodulatory drug and bortezomib. Is it acceptable to use parametric curves fitted to the Kaplan-Meier curves rather than the trial data and then extrapolate the data?

Hazard ratios

- The company presents progression-free survival and overall survival as hazard ratios developed using an Unadjusted Cox method. Curves that cross or converge violate the proportional hazards assumptions (see Table 26a of company main submission). The ERG commented that the data does not support the proportional hazards assumption. Are the hazard ratios for panobinostat plus bortezomib and dexamethasone compared with lenalidomide plus dexamethasone credible?

Health-related quality of life

- Do the Committee consider the following assumptions and sources of utility values suitable?

- Heath-related quality of life data were collected during the PANORAMA-1 trial, for treatment until disease progression and for discontinuation but was not collected during the treatment free interval.
- No utility data were available for lenalidomide plus dexamethasone treatment. The company assumed it to be the same as that for bortezomib plus dexamethasone in PANORAMA in its base case. In a scenario analysis it was assumed to be the same as the utility value associated with the progression-free, no treatment health state.
- In the economic model mean values rather than median values were used despite the skewed distribution of the mapped utilities.

Plausible ICER

- The company considered that the result of the Unadjusted Cox method (subgroup of at least 2 previous treatments including an immunomodulatory drug and bortezomib) show only a small incremental QALY gain of 0.0518 but is the calculation of the QALYs using this method appropriate?
  - The company's base case ICER for the population with the positive CHMP opinion when comparing panobinostat plus bortezomib and dexamethasone with lenalidomide plus dexamethasone shows that panobinostat dominates the comparator (lenalidomide plus dexamethasone).

End-of-life

- Does panobinostat meet the end-of-life criteria?
- The company stated that:
  - Patients have a short life expectancy of less than 24 months (a median overall survival of 1.4 years when the second-line treatment was a bortezomib-based regimen)
  - Population approximately 1300
  - Overall survival data from the PANORAMA-1 trial are not yet mature but the most recent analysis reported a median overall survival of 2.86 months.

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of panobinostat within its marketing authorisation for treating multiple myeloma in people who have received at least 1 prior therapy. The positive CHMP opinion (received 25 June 2015) was based on a subgroup of people who have had at least 2 previous treatments including an immunomodulatory drug and bortezomib.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	People with multiple myeloma who have received at least 1 prior therapy	As described in the final scope but also included people with multiple myeloma who have received at least two prior lines of treatment including an immunomodulatory drug and bortezomib.	NA	The ERG was concerned that the company had used a subgroup of patients who had received at least 2 previous treatments but these weren't necessarily an immunomodulatory treatment and bortezomib
Int.	Panobinostat in combination with bortezomib and dexamethasone			
Com.	After 1 prior therapy: • bortezomib monotherapy • bortezomib plus dexamethasone After 2 or more prior therapies: • bortezomib plus dexamethasone • lenalidomide plus dexamethasone • combination chemotherapy	After 1 prior therapy: • Bortezomib plus dexamethasone After 2 or more prior therapies including an immunomodulatory drug and bortezomib: • Lenalidomide plus dexamethasone	The company considered there was insufficient data to compare panobinostat plus bortezomib and dexamethasone with the comparators excluded from the submission. The company considers that the comparators	The ERG considered the company's rationale for not including all the comparators in the scope, after 2 or more prior therapies, was not clear

	regimens with, for example, melphalan and doxorubicin, thalidomide and corticosteroids		it has chosen are the most relevant for current clinical practice in England. The company stated that bortezomib in combination with dexamethasone is not available in the UK after prior bortezomib	
Out.	• progression-free survival • overall survival • response rates • time to next treatment • adverse effects of treatment • health-related quality of life	All were included except 'time to next treatment'. Instead the company included 'treatment-free interval' as an outcome measure.	Treatment-free interval, the time period between discontinuation of panobinostat or the comparator and starting the next line of therapy on disease progression, provides a measure of the benefit of therapy to patients. During this period patients experience a better quality of life being off treatment and without progressive disease	The ERG was unsure why the company did not include time to next treatment as an outcome

2 The technology and the treatment pathway

2.1 Panobinostat (Farydak, Novartis Pharmaceuticals UK) is an oral potent histone deacetylase inhibitor that disrupts a key mechanism in the transformation of normal cells to cancerous cells and selectively targets tumour cells for cell death. Panobinostat received a positive CHMP

opinion as follows ‘panobinostat, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent’.

2.2 Multiple myeloma is an incurable disease. The main aims of therapy are to prolong survival, and to maintain a good quality of life by controlling the disease and relieving symptoms. Autologous stem-cell transplantation with high-dose chemotherapy may be suitable for people in good general health. When stem-cell transplantation is not suitable, NICE technology appraisal guidance 228 recommends triple therapy thalidomide or bortezomib (only in people unable to tolerate or with contraindications to thalidomide) in combination with an alkylating agent (melphalan, cyclophosphamide) and a corticosteroid (prednisolone, dexamethasone). The NICE technology appraisal guidance 311 recommends bortezomib in combination with dexamethasone or dexamethasone and thalidomide for induction treatment of adults with previously untreated multiple myeloma.

2.3 Following first-line treatment, subsequent therapy is influenced by the number and nature of previous treatment, response to previous treatment, duration of remission, comorbidities and patient preference. For second-line treatment, NICE technology appraisal guidance 129 recommends bortezomib monotherapy as an option for people who are at first relapse having received 1 prior therapy and who have undergone, or are unsuitable for bone marrow transplantation. In people who have received at least 2 prior therapies, NICE technology appraisal guidance 171 recommends lenalidomide in combination with dexamethasone. Other subsequent treatment options may include repeating high-dose chemotherapy or chemotherapy with alkylating agents and anthracyclines, thalidomide and corticosteroids. The treatment pathway for multiple myeloma and the company’s anticipated position for panobinostat is shown in Figure 1.

Figure 1. The treatment pathway for multiple myeloma and the company's anticipated position for panobinostat (adapted from NICE pathway: 'Blood and bone marrow cancers: multiple myeloma and company submission page 33).

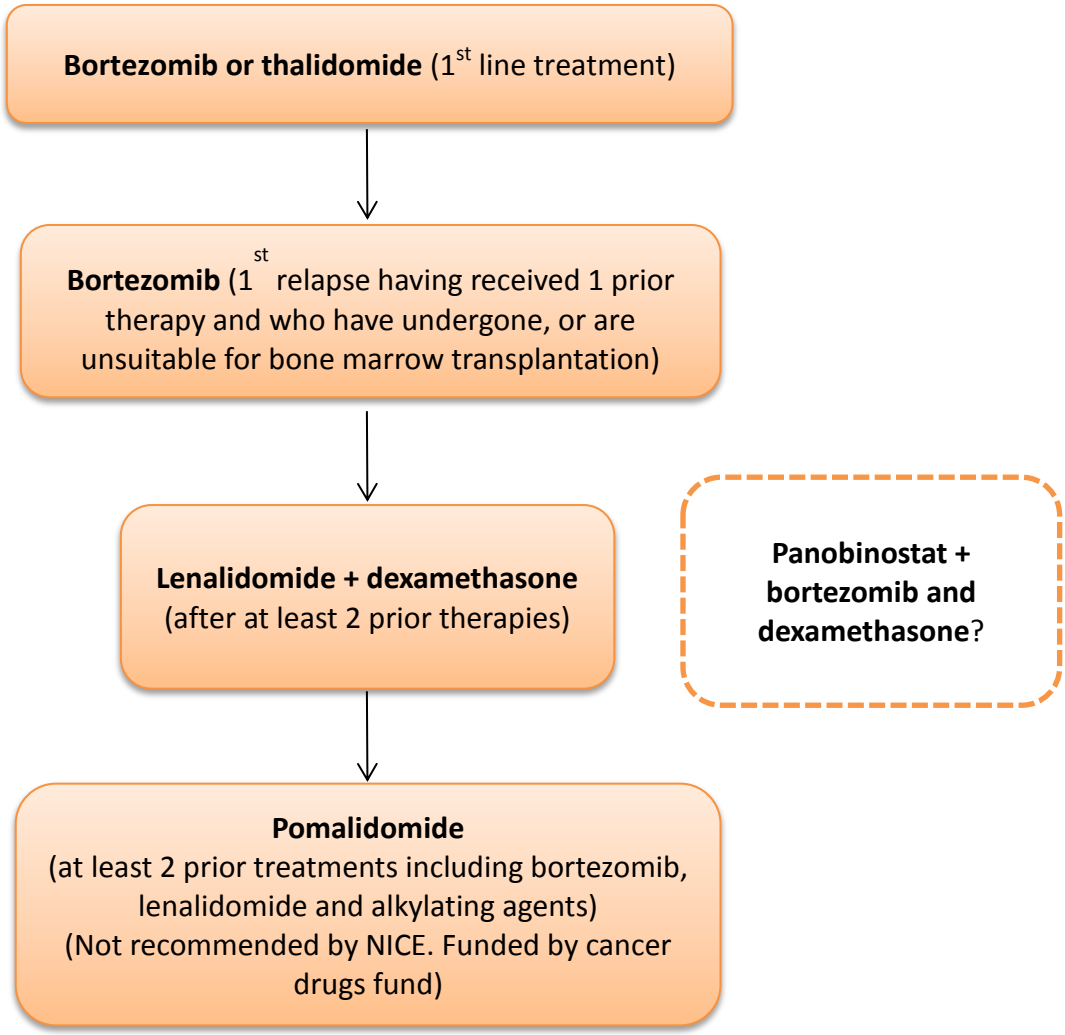


Table 2 Technology

	Panobinostat	Bortezomib	Dexamethasone	Lenalidomide
Marketing authorisation	Positive CHMP opinion received on 25th June: Panobinostat, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent	Bortezomib as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation.	Oncological disorders: including malignant lymphoma (Hodgkin's disease, non-Hodgkin's lymphoma)	Lenalidomide in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy
Administration method	Oral	Subcutaneous injection	Oral or subcutaneous injection	Oral
Cost information	20 mg cap price = £776 15 mg cap price = £582 10 mg cap price = £582 (Price has been confirmed with DH, July 2015) Initial treatment involves eight 3 week cycles with panobinostat taken on days 1, 3, 5, 8, 10 and 12. If patients benefit from the treatment then 4 additional cycles of 6 week cycles are	3.5 mg vial = £762.38 [BNF online accessed May 2015]	28-tab pack (500 mg) = £59.52; 50-tab pack (2 mg) = £46.39, 100-tab pack (2 mg) = £78.00 Oral solution, 2 mg/5 ml, price 75mL= £32.50, 150 ml = £42.30. Injection 3.8 mg/ml, 1 ml vial = £1.99. [BNF online accessed	21 cap pack (2.5 mg) = £3426.00 21-cap pack (5 mg) = £3570.00 21-cap pack (10 mg) = £3780.00 21-cap pack (15 mg) = £3969.00 21-cap pack (25 mg) = £4368.00

	recommended by the company. When the patient access scheme was incorporated, the drug cost for panobinostat was [redacted]		May 2015]	

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 Clinical experts and professional groups stated that the majority of people in the UK would receive bortezomib-based treatments, outside of clinical trials, at the time of first relapse and lenalidomide-based therapy at the time of second relapse. If a patient did not receive bortezomib at first relapse they are able to receive it at subsequent relapse from the Cancer Drugs Fund. Subsequent treatments would include pomalidomide and bendamustine, thalidomide and alkylating agents (melphalan and cyclophosphamide).

3.2 Patient and carer organisations stated that people with myeloma experience severe bone pain, frequently in the back, which can reduce quality of life. Other symptoms of multiple myeloma can include loss of appetite, feeling sick and constipation, tiredness and lethargy reducing ability to carry out everyday activities, weight loss, unusual bruising and bleeding, frequent infections and kidney problems and bone fractures. People with multiple myeloma can experience relapses and remissions, impacting physical and psychological wellbeing, causing stress for the patient, families, carers and employers. Patients are on life-long treatment for myeloma and decreasing treatment options can be stressful with patients needing effective treatments, at each relapse. Patient preference for treatment administration differs with some preferring not to regularly travel to hospital and others enjoying the opportunity to meet other patients and regularly see clinicians. Patients also have different experiences with different treatments and they consider it important to have a range of options available. The most important considerations for patients include long term survival, a better quality of life, with reduced side effects and a reduction in the length of time needed for treatment due to longer remission periods, low or undetectable paraprotein levels, and prolonged life.

3.3 Panobinostat would likely be used where bortezomib and dexamethasone are currently used, for relapsed myeloma where 1 or 2 prior therapies have already been received.

3.4 A patient and carer group thought that panobinostat would provide an innovative option for treatment using a new mechanism of action and that it may not have a risk of thrombo-embolism and may not cause neurotoxicity. However, the possible side effect profile of panobinostat, particularly the increased number of adverse events such as diarrhoea, low blood counts, neuropathy and nausea could be a concern as these can increase the number of hospital visits needed, impacting peoples' lives both emotionally, with reliance on family and carers for assistance and financially. One patient and carer group and a clinical expert noted that patients and clinicians considered it possible to adequately manage the side effects of panobinostat treatment through communication and supportive care and some patients are willing to tolerate an increased side-effect profile when there is an improvement in outcomes. A disadvantage noted was that bortezomib is administered either subcutaneously or intravenously, requiring a hospital visit alongside the oral panobinostat treatment. However, it was also stated that as panobinostat is not a 'treat until progression' treatment, patients can expect a treatment free interval at the end of treatment cycles when the disease has responded.

3.5 A clinical expert and professional group stated that panobinostat should be used in specialist clinics in tertiary care but no additional administration would be required as it is an oral treatment. A clinical expert stated that healthcare professionals would need some training about the toxicity profile of panobinostat but that no additional facilities or equipment would be required.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company included 1 randomised controlled trial, PANORAMA-1, which compares panobinostat, bortezomib and dexamethasone with bortezomib and dexamethasone in patients who have relapsed or relapsed and refractory multiple myeloma and have received between 1 and 3 prior treatments. The trial involved 215 centres in 34 countries with 30 centres based in the UK. Patients (n=768) were randomly assigned 1:1 to either panobinostat (n=387) or placebo (n=381) (both in combination with bortezomib and dexamethasone) and were stratified by number of previous treatments and previous bortezomib treatment. The baseline demographics and pathological characteristics were similar in the two treatment groups. Approximately one third (35% in the intervention group and 37% in the comparator group) of people in the trial had relapsed and refractory multiple myeloma and approximately one half of people had received greater than 2 lines of treatment (48.8% for the intervention group and 48% for the comparator group).

4.2 Treatment allocation in the trial was blinded and no crossover occurred. The trial was divided into phase 1 (24 weeks of 8 cycles of 21 days treatment) and phase 2 (24 weeks of 4 cycles of 42 days duration). During phase 1, in week 1 and 2 of each cycle patients received either panobinostat (20 mg) or placebo 3 times a week, bortezomib (1.3 mg/m^2) twice a week and dexamethasone (20 mg) 4 times a week. There was no treatment in the third week of the cycle. Patients moved onto phase 2 if they had experienced clinical benefit, defined as at least no change on day 1 of cycle 8 (as assessed by the modified European Group for Blood and Marrow Transplantation criteria). Phase 2 was identical to phase 1 except that bortezomib was administered once a week.

4.3 Patients who could not tolerate panobinostat, placebo or bortezomib were required to permanently discontinue treatment, but were followed for

disease assessment and survival. Patients who could not tolerate dexamethasone were permitted to continue treatment without dexamethasone.

4.4 The primary outcome was progression-free survival with response assessed at 3 week intervals during the treatment phases and at 6 week intervals thereafter. Progression-free survival (as assessed by the investigators on the basis of the modified European Group for Blood and Bone Marrow Transplant criteria) was defined as the time from randomisation until documented disease progression, relapse from complete response, or death, whichever came first. The final analysis for progression-free survival was performed at the data cut-off on 10th September 2013 and at median follow-up of 31 months. Progression-free survival observations were censored at the date of the last response assessment for people who had either not progressed or received a different treatment.

4.5 The key secondary outcome was overall survival which was defined as the time from randomisation to death from any cause. An interim overall survival analysis was conducted at the time of the final progression-free survival analysis and a second analysis was carried out when 86.5% of the 415 events, required for the final overall survival analysis, were observed. The final analysis will be carried out when all 415 overall survival events have been observed. Other secondary outcomes included overall response rate (complete response, near complete response and partial response), time to progression, time to response and duration of response, safety and health related quality-of-life (including European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-MY20 and Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group – Neurotoxicity).

4.6 The trial had a number of pre-planned subgroups including number of prior lines of therapy (1, 2 or 3) identified by the type and number of

previous treatments. The subgroups included patients that had received 1 immunomodulatory drug plus bortezomib (n=193, 25% of the PANORAMA-1 population), patients who had received at least 2 prior lines of treatment including 1 immunomodulatory drug plus bortezomib (n=147, 19% of the trial population) and patients who had received 2 or 3 previous lines of treatment (n=371, 48.3% of the trial population). A higher proportion of patients in these subgroups had relapsed and refractory disease (51% compared with 36%) and the median time to diagnosis and entering the study was longer (45 and 40 months in previous bortezomib and immunomodulatory treatment subgroups compared with 37 and 39 months in the overall population for the panobinostat and comparator group respectively). In these subgroups 76.1% of patients had received at least 2 previous treatments and a higher proportion of patients had received stem cell transplantation (71%) compared with the overall population (57.2%).

4.7 The company also included 2 published non-randomised controlled trials (PANORAMA-2 and B2207) to provide further evidence for panobinostat plus bortezomib and dexamethasone compared with bortezomib and dexamethasone. The PANORAMA-2 trial population were patients with relapsed and bortezomib-refractory multiple myeloma (n=55) and compared the safety and efficacy of the panobinostat intervention group to the comparator treatment. The patients in the B2207 trial had relapsed or relapsed or refractory multiple myeloma (n=62) and was designed to determine the maximum tolerated dose, evaluate safety, pharmacodynamics and pharmacokinetics and efficacy of panobinostat.

ERG comments

4.8 The ERG considered that all relevant trials were included in the company's submission. The ERG considered that the evidence submitted by the company generally reflected the decision problem. However the ERG was concerned that the terms relapsed and relapsed and refractory were confused within the company's submission as use of the term has

been mixed across the submission describing both patients who had received 1 prior treatment and those that had received at least 2. The ERG concluded that relapsed and refractory should be used for people who had received at least 2 previous treatments.

4.9 The ERG was concerned that patients in the PANORAMA-1 trial were able to receive bortezomib up to cycle 12, whereas in clinical practice in the UK patients would only receive bortezomib up to and including cycle 8.

Clinical trial results

4.10 The company presented results for the full population from PANORAMA-1 and also for the subgroup of people who have had at least 2 previous treatments including an immunomodulatory drug and bortezomib since the submission was prepared before the CHMP positive opinion was received. The positive CHMP opinion was based on the population in the subgroup and so the results will mainly focus on the subgroup. Details of the full population can be found in the company submission.

Full population

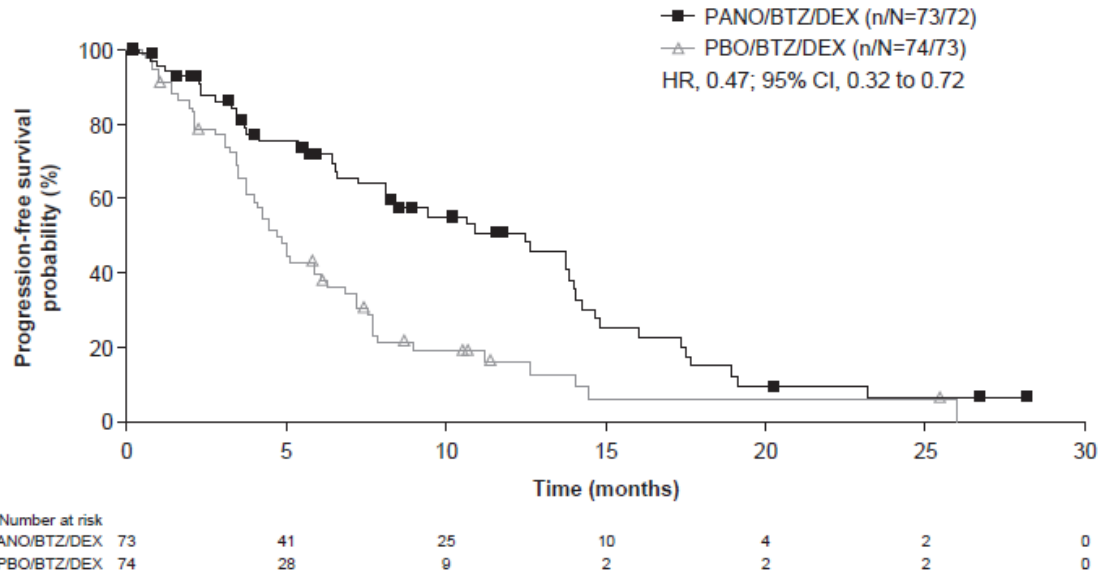
4.11 The investigator assessed median progression-free survival, which increased from 8.1 months for the placebo plus bortezomib and dexamethasone group to 12.0 months for the panobinostat plus bortezomib and dexamethasone group ($p<0.0001$). The independent assessment of progression-free survival also reported a statistically significant improvement for the panobinostat group (11.99 months compared with 8.31 months; $p<0.001$). Overall response rate was the same for the 2 groups but complete response and near complete response was statistically significantly higher ($p=0.00006$) for the panobinostat plus bortezomib and dexamethasone group when compared with the placebo group. The risk of progression was statistically significantly reduced by 37% in patients treated with panobinostat plus bortezomib and dexamethasone compared with the placebo group for

both the investigator and independent assessment. Full outcome details can be found in the company submission, Table 12, page 66.

Subgroup analyses - people who had previously received at least 2 treatments including an immunomodulatory drug and bortezomib

4.12 In the PANORAMA-1 trial, patients receiving panobinostat plus bortezomib and dexamethasone, who had previously received at least 2 treatments including an immunomodulatory drug and bortezomib, had a median progression-free survival extension of 7.8 months compared with placebo, representing a 53% reduction in the risk of progression (Figure 2).

Figure 2 Progression-free survival in PANORAMA-1 for people who had received at least 2 prior treatments including an immunomodulatory drug and bortezomib (data cut-off September 2013) (taken from CS, Figure 26, page 91)



4.13 Overall survival was extended by [redacted] months from [redacted] months in the placebo group to [redacted] months in the panobinostat plus bortezomib and dexamethasone group (Figure 3).

Figure 3. Overall survival in PANORAMA-1 for people who had received at least 2 prior treatments including an immunomodulatory drug and bortezomib (2nd interim analysis) (From CS, Figure 27, page 91).

4.14 Overall response rate and complete response/near complete response were increased in the panobinostat plus bortezomib and dexamethasone group compared with placebo (Table 3). Details of other outcomes were not reported in the company's submission.

Table 3. Clinical trial outcomes for people who had received at least 2 prior treatments including an immunomodulatory drug and bortezomib (from CS Table 19, page 85)

	Prior IMiD plus BTZ and ≥ 2 prior lines of treatment	
	Panobinostat plus lenolidamide and dexamethasone n = 73	**Placebo plus lenolidamide and dexamethasone n = 74**
Median PFS, months HR (95% CI)	12.5 0.47 (0.32 to 0.72)	4.7
Median OS, months HR (95% CI)	[redacted] [redacted]	[redacted]
Overall response rate, % (95% CI)	58.9 (46.8 to 70.3)	39.2 (28.0 to 51.2)
CR/nCR, % (95% CI)	21.9 (13.1 to 33.1)	8.1 (3.0 to 16.8)
Abbreviations: CR; complete response, nCR; near complete response,		

ERG comments

4.15 The ERG considered that the population in the PANORAMA-1 trial generally reflected relapsed and refractory multiple myeloma patients in the UK. However, the ERG considered the population in the PANORAMA-1 trial to be younger than most multiple myeloma patients in the UK (the median age in PANORAMA-1 was 63 years (for both arms; ranging between 28 to 84 for PANO group and 32-83 in the control arm). It also considered that people in the trial received bortezomib up to cycle 16 but in UK clinical practice patients do not receive bortezomib beyond cycle 8, with a stopping rule at 4 cycles if no response was seen. The ERG noted that in the PANORAMA-1 trial, patients were administered bortezomib intravenously, following guidelines, but that in UK clinical practice it is becoming more common to administer bortezomib subcutaneously.

4.16 The ERG noted that the population of interest were people with relapsed or relapsed and refractory multiple myeloma who had received at least 2 previous treatments including an immunomodulatory drug and bortezomib. This subgroup was included in the trial and was either treated

with panobinostat plus bortezomib and dexamethasone or bortezomib plus dexamethasone. However the company did not include this comparison in its submission, only a comparison with lenalidomide plus dexamethasone (see section 4.17 onwards).

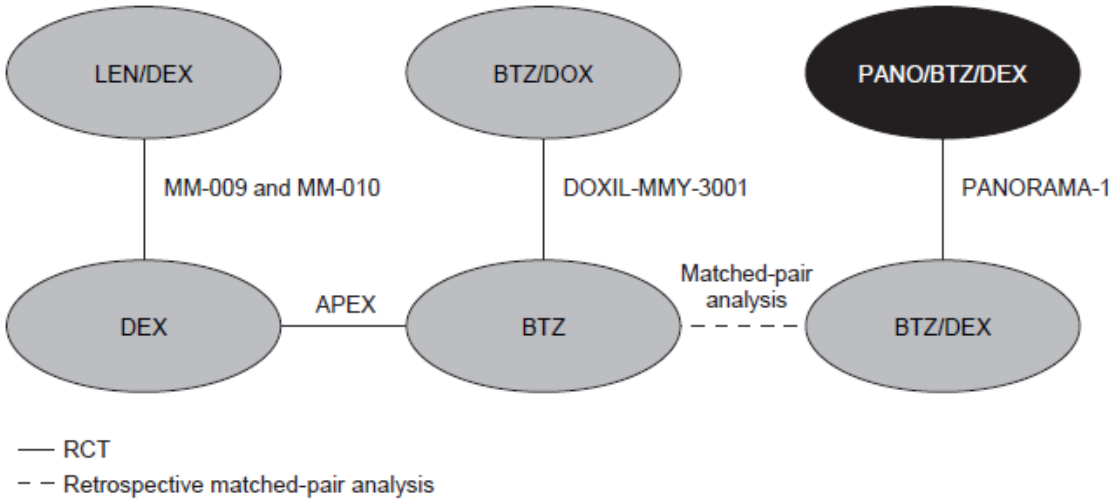
Indirect comparison

4.17 An indirect comparison was performed by the company, for both the full population and the subgroup that received the positive CHMP opinion, to compare panobinostat plus bortezomib and dexamethasone with bortezomib, thalidomide, lenalidomide, dexamethasone, and pegylated liposomal doxorubicin. Two different comparisons were carried out: the first was a comparison of efficacy outcomes (median progression-free survival and overall survival) for the treatment arms of interest in relevant trials without any adjustment for differences in design between the trials (a naïve comparison) and the second, a comparison using matching adjusted indirect treatment comparison methodology. The following trials were included in the indirect comparison:

- PANORAMA-1, the pivotal phase 3 study for panobinostat (n = 768), provides data for PANO/BTZ/DEX versus BTZ/DEX.
- Pooled data from the MM-009 and MM-010 trials, the two pivotal phase 3 studies for lenalidomide (n = 704) provide data for LEN/DEX versus dexamethasone.
- DOXIL-MMY-3001, a phase 3 study assessing the benefit of the addition of doxorubicin (n = 646), provides data for BTZ/DOX versus bortezomib.
- APEX, the pivotal phase 3 trial for bortezomib (n = 669), provides data for bortezomib versus high-dose dexamethasone.
- A retrospective matched-pair analysis of data for 218 patients provides data for BTZ/DEX versus bortezomib

The final evidence network included lenalidomide plus dexamethasone, dexamethasone, bortezomib, bortezomib plus doxorubicin and bortezomib plus dexamethasone as comparators (see Figure 4).

Figure 4. Evidence network for the common comparator method (taken from CS page 95)



Abbreviations: BTZ, bortezomib; DEX, dexamethasone; DOX, doxorubicin; LEN, lenalidomide; PANO, panobinostat; RCT, randomised controlled trial.

4.18 Four different indirect treatment comparison methods were used (common comparators method, naïve comparison, unadjusted cox and matching adjusted indirect treatment comparison).

4.19 The common comparators method replies on the randomisation within each trial where treatments were compared directly and using the relative effect measures for the analyses and separates out true effect and placebo effects. Panobinostat plus bortezomib and dexamethasone was chosen as the reference treatment for ease of comparison of the results and their interpretation. The models were conducted using Markov chain Monte Carlo simulation methods. Vague priors (not favouring one value over another) were imposed and 360,000 iterations were run with the first 60,000 iterations being discarded. Every 30th simulation was retained to ensure independence between the simulations. The results for the subgroup of people who had received two prior treatments including an immunomodulatory drug and bortezomib are shown in Table 4.

Table 4. Summary of the results of the indirect treatment comparison for the subpopulation population (common comparators method: adapted from CS Table 24, page 101)

	Panobinostat plus bortezomib and dexamethasone	**Lenalidomide plus dexamethasone**
Progression-free survival hazard ratio (± CrI)[a]	1.00	1.87 (0.87 to 3.49)
Time to progression hazard ratio (± CrI)[b]	1.00	1.91 (0.90 to 3.60)
Complete response/ near complete response hazard ratio (± CrI)[c]	1.00	0.49 (0.08 to 1.63)
Overall survival hazard ratio (± CrI)[d]	1.00	1.22 (0.53 to 2.39)

[a] Values > 1 indicate shorter PFS than for PANO/BTZ/DEX.
[b] Values > 1 indicate shorter TTP than for PANO/BTZ/DEX.
[c] Values < 1 indicate lower rate of CR + nCR than for PANO/BTZ/DEX.
[d] Values > 1 indicate shorter OS than for PANO/BTZ/DEX.
CrI; credible interval

4.20 Results of the naïve comparison indicated that the progression-free survival and overall survival for panobinostat plus bortezomib and dexamethasone compared with lenalidomide plus dexamethasone was similar, assuming exponential survival models for the two outcomes. Uncertainty around the 2 outcomes was not reported and therefore uncertainty around the hazard ratios could not be reported (see Table 5).

Table 5. Naive comparison results for people who had received 2 prior treatments including an immunomodulatory drug and bortezomib (Taken from CS Table 25 b, page 103).

	PANO/BTZ/DEX	LEN/DEX	Hazard ratio (LEN/DEX versus PANO/BTZ/DEX)
PFS, months	11.3	9.5	1.19
OS, months	[redacted]	35.8	0.959
BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; OS, overall survival; PANO, panobinostat; PFS, progression-free survival.			

4.21 The Unadjusted Cox method was also used to estimate hazard ratios for progression-free survival and overall survival when comparing with lenalidomide plus dexamethasone. Patient level data from the PANORAMA-1 trial was used for the panobinostat group whereas patient level data were simulated for the lenalidomide group. For the subpopulation of patients who had received at least 2 previous treatments the hazard ratio for progression-free survival was 1.061 and for overall survival was 1.075.

4.22 For the matching adjusted indirect treatment comparison patient level data for panobinostat plus bortezomib and dexamethasone and lenalidomide plus dexamethasone was required. Patient level data from the PANORAMA-1 trial was used for the panobinostat group and data from the pooled analysis of the MM-009 and MM-010 studies and a subpopulation from Stadtmauer et al 2009 were used for the lenalidomide plus dexamethasone group. Individual patient level data from the PANORAMA-1 trial were reweighted such that the average/median baseline characteristics matched those reported from the MM-009 and MM-010 trials. These variables included age, sex, time since diagnosis, ECOG score, prior number of treatments, prior treatments (immunomodulatory drugs and bortezomib) and serum ß2-microglobulin level. For the subpopulation of patients who had received at least 2

previous treatments the hazard ratio for progression-free survival was 1.108 and for overall survival was 1.413.

ERG comments

4.23 The ERG noted that the company had included 5 studies in its indirect comparison but was unsure how these studies had been identified. The patient characteristics were similar in terms of median age, disease duration, proportion of patients with 1 previous line of therapy, except for the matched pairs analysis, where only patients with 1 previous line of therapy were included. The ERG determined that statistical assessment of heterogeneity was not conducted because there was only 1 trial per treatment except for lenalidomide plus dexamethasone, which included 2 trials (MM-009 and MM-010). The ERG commented that population in MM-009 were mainly from the USA and Canada so may not be completely generalizable to the UK. MM-010 recruited people from Europe so was more generalisable.

4.24 The ERG considered that generally the studies included in the indirect comparison were of similar design including patient selection criteria but that the company had directly compared results such as time to progression/progression-free survival, which may include confounding factors between the populations making a direct comparison inappropriate. This also means that all unadjusted analyses for baseline differences are likely to be biased and assume proportional hazards and that the only adjusted analyses, MAIC method, has low statistical power.

4.25 The ERG noted that the subgroup of interest, people who had received at least 2 previous line of treatment were not analysed in the indirect comparison using the common comparisons analysis but that the company did not explain why this was the case. The ERG also noted that the populations included in the trials were broader than the subgroup of interest.

4.26 The ERG was unable to confirm the use of individual patient level data simulated by the company for lenalidomide plus dexamethasone because details of the method were not provided by the company.

4.27 The ERG lacked confidence in the estimations of the hazard ratios constructed for progression-free survival and overall survival for the comparison of panobinostat plus bortezomib and dexamethasone with lenalidomide plus dexamethasone using the Unadjusted Cox method.

Adverse effects of treatment

4.28 No trials were identified which primarily assessed safety of panobinostat plus bortezomib and dexamethasone. Safety data have been reported for the PANORAMA-1 trial. Patients were followed for a median of 31 months. The numbers of patients in the safety set who required at least one dose change in the panobinostat plus bortezomib and dexamethasone group were 194 (51%) for panobinostat, 231 (61%) for bortezomib and 93 (24%) for dexamethasone; in the placebo plus bortezomib and dexamethasone group the equivalent numbers were 86 (23%) for placebo, 158 (42%) for bortezomib and 65 (17%) for dexamethasone. The most frequent (≥ 2%) adverse events leading to treatment discontinuation were diarrhoea, fatigue, asthenia and peripheral neuropathy in the panobinostat plus bortezomib and dexamethasone group and fatigue and pneumonia in the placebo plus bortezomib and dexamethasone group. The incidence of adverse events was much lower during cycles 9 to 12 (treatment phase 2) when bortezomib and dexamethasone were administered less frequently. Adverse events occurring in either treatment phase 1 or 2 are shown in Table 6.

Table 6. Adverse events occurring in >30% of patients in either treatment group according to treatment phase in PANORAMA-1 (taken from CS, Table 35, page 120)

	Treatment phase 1		Treatment phase 2	
AE any grade/grade 3/4, %	PANO/BTZ/DEX (n = 381)	PBO/BTZ/DEX (n = 377)	PANO/BTZ/DEX (n = 168)[a]	PBO/BTZ/DEX (n = 193)[a]
Diarrhoea	65.9/24.1	38.2/8.0	29.8/7.1	20.2/0
Thrombocytopenia	64.3/56.7	40.1/24.4	18.5/6.0	5.2/1.0
Anaemia	39.9/15.5	31.8/15.1	13.7/3.0	9.3/3.6
Fatigue	39.6/16.3	28.9/8.8	8.9/1.8	4.7/0
Nausea	35.2/5.5	19.4/0.5	5.4/0	4.7/0
Peripheral neuropathy	29.4/6.0	32.9/4.8	6.5/3.0	11.9/1.6
Constipation	26.0/1.0	31.8/1.1	3.6/0	5.7/0

[a]One patient randomly assigned to receive panobinostat was given placebo during cycles 1 and 2 because of an allocation error; the patient was subsequently given panobinostat from cycle 3 until discontinuation of treatment but was included in the placebo group for the safety analysis.
Abbreviations:
AE, adverse event; BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; PBO, placebo

4.29 The safety profile of the subgroup of patients who had received prior immunomodulatory drugs and bortezomib was similar to the overall study population. The number of on-treatment deaths was comparable between the two treatment groups (panobinostat plus bortezomib and dexamethasone, n = 6, 6.5%; placebo plus bortezomib and dexamethasone, n = 5, 5.1%) of which 0% and 2%, respectively, were attributed to disease progression.

5 Cost-effectiveness evidence

Model structure

5.1 The company developed 2 models – one for the full population in PANORAMA-1 and a separate model for the subgroup of people who had received 2 prior treatments including an immunomodulatory drug and bortezomib (the subgroup that received a positive CHMP opinion and will

therefore receive the likely marketing authorisation). From this point onwards only the model for the subgroup containing people who had received at least 2 previous treatments including an immunomodulatory drug and bortezomib will be discussed.

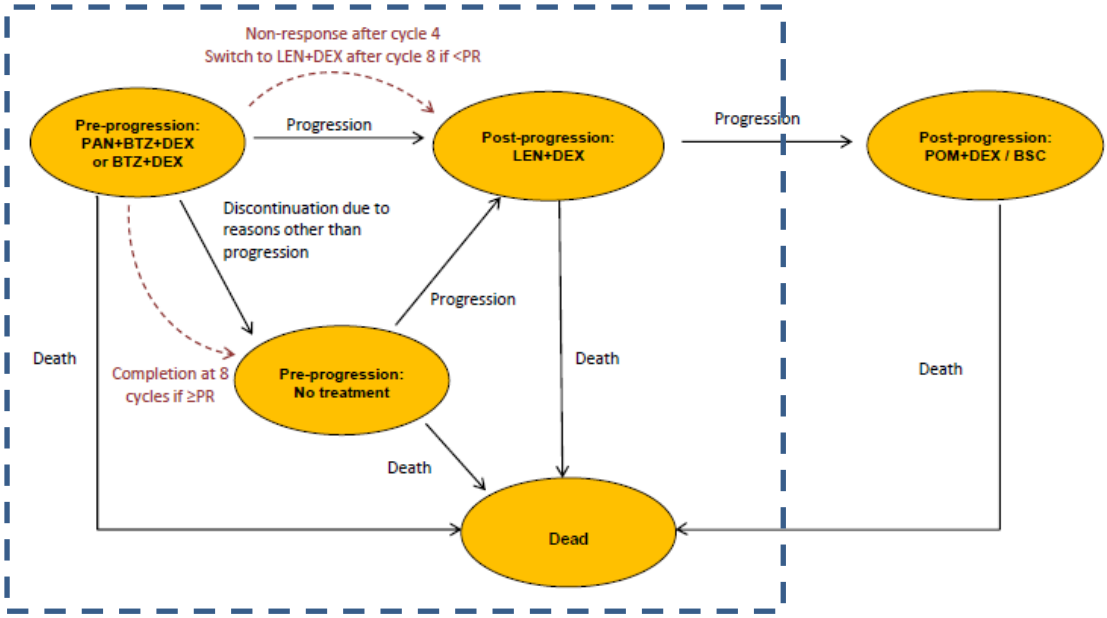
5.2 The company developed a decision analytic semi-Markov model consisting of 3 health states: pre-progression, post-progression and death. The time horizon of the model was 25 years and the cycle length was 3 weeks with a half-cycle correction applied. Discounting of 3.5% was incorporated for both effects and costs and the analysis was carried out from the perspective of the NHS and personal social services.

Model details

5.3 The model assumes that patients receive either panobinostat plus bortezomib and dexamethasone or lenalidomide and dexamethasone (see Figure *5*). Patient flow within the model is as follows:

- **Pre progression, Tx1 health state** - Patients receive either panobinostat with bortezomib and dexamethasone or lenalidomide plus dexamethasone treatment. Once receiving therapy, patients can experience early discontinuation of treatment because of progression or relapse, early discontinuation of treatment and reasons other than progression, and death
- **Pre-progression, no Tx1 health state** – After monitoring patients can move to either the progression or death state. If they move to the progression state they will receive further treatment because they will have moved to the post-progression state.
- **Post-progression health state** – Patients are presumed to receive post-progression treatment until death and no further treatment is allowed in the model
- **Death health state** - Patients can move to this health state at any point during the model.

Figure 5. Structure of the decision analytic semi-Markov model



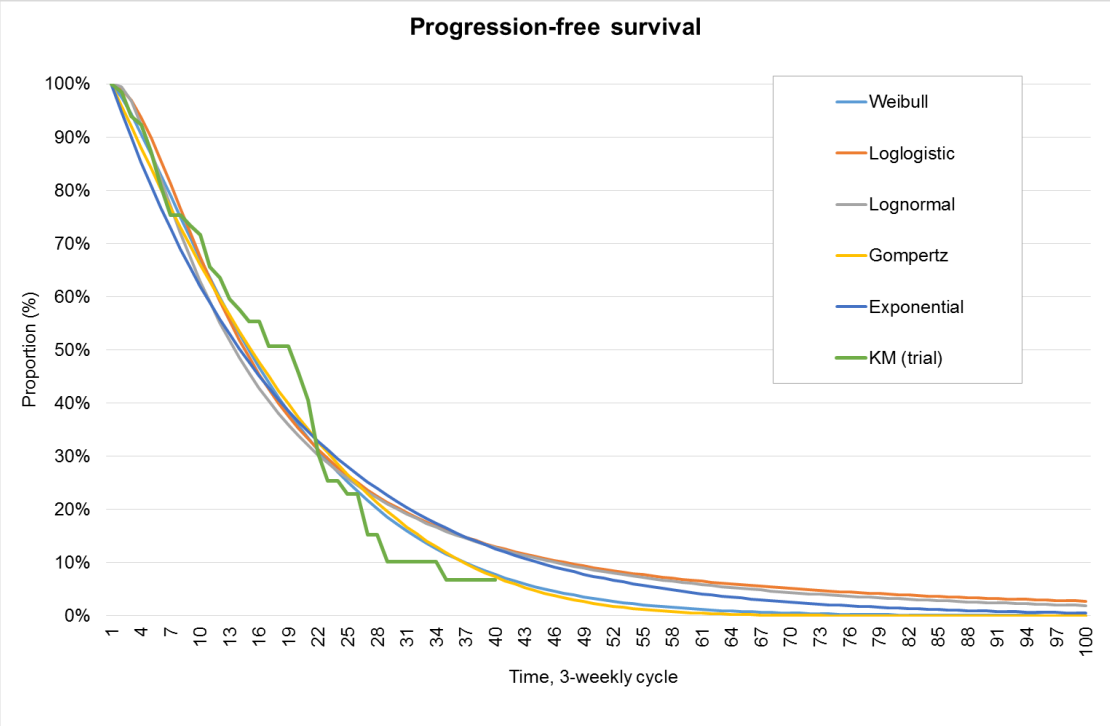
Red arrows apply only to patients who receive bortezomib plus dexamethasone. Patients who complete panobinostat plus bortezomib and dexamethasone treatment transition to the 'Pre-progression, No treatment health state'. Blue dashed line represents structure of the model for the subgroup who received 2 or more previous treatments. Abbreviations: BSC, best supportive care; BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PAN, panobinostat; POM, pomalidomide; PR, partial response

5.4 The transition probabilities for panobinostat plus bortezomib and dexamethasone were derived from post hoc patient level data from the PANORAMA-1 trial and included progression-free survival, exposure of treatment and overall survival.

5.5 The probabilities for risk of progression or pre-progression death (based on progression-free survival data), risk of treatment discontinuation (based on exposure to treatment data) and risk of death (based on overall survival data) were generated by fitting parametric curves to the Kaplan-Meier data to estimate transition probabilities for panobinostat plus bortezomib and dexamethasone (see section 5.6). Time since randomisation until progression or death or censoring was considered as exposure time.

5.6 Five distributions (exponential, Weibull, log-logistic, log-normal and Gompertz) were fitted on the individual patient-level progression-free survival data to extrapolate the curves beyond the trial period and to derive transition probabilities (see Figure 6).

Figure 6. Progression-free survival Kaplan-Meier curve and fitted parametric models for people who had received 2 prior treatments including an immunomodulatory drugs and bortezomib (taken from CS, appendix 17, Figure 2, page 22)



5.7 The risk of treatment discontinuation in a 3 week cycle, to determine the proportion of patients who are on or off treatment, was estimated using patient level discontinuation data from the PANORAMA-1 trial. The length of treatment exposure for a patient was considered the time to treatment discontinuation. All patients discontinued treatment before or at the time of a progression-free survival event so no patient was censored. The median treatment duration was 4.2 months (6.1 cycles) for people who have received at least 2 previous treatments including an immunomodulatory drug and bortezomib. The exponential distribution was judged to provide

the best model for panobinostat plus bortezomib and dexamethasone and was selected for the base case model. The curves were not extrapolated because all patients discontinued treatment.

5.8 The transition probabilities for the risk of death (either progression or pre-progression death) in a given cycle were estimated using patient level data from the PANORAMA-1 trial, once parametric curves had been fitted. For the overall survival analysis, time since randomisation until death (an event) or censoring was treated as exposure time. Patients were censored at the last contact date if they were lost to follow-up for survival status measurements. The company considered the Gompertz distribution to provide the best model for panobinostat plus bortezomib and dexamethasone.

Mapping of health-related quality of life

5.9 Patients in the PANORAMA-1 trial completed an EORTC QLQ-C30 questionnaire which was mapped to obtain the corresponding EQ-5D utility value. No adjustment was applied, in case mapped values were higher (or lower) than the maximum (or minimum) EQ-5D utility score. Adjustment to baseline patient characteristics was not feasible. Cycle-specific as well as overall average and median utility values were estimated for the treatment arms. The values are shown below (Table *7*).

5.10 No utility data were available for lenalidomide plus dexamethasone treatment in people who have received at least 2 previous treatments including an immunomodulatory drug and bortezomib, so 2 scenarios were explored. In the first, the utility value for lenalidomide plus dexamethasone treatment was assumed to be the same as that for bortezomib plus dexamethasone and in the second scenario it was assumed to be the same as the utility value associated with the progression-free no treatment health state. The first scenario was considered for the base case analysis.

5.11 In PANORAMA-1, health-related quality of life was not measured in patients who discontinued treatment or after completion of treatment. Therefore, the utility value associated with the treatment–free interval and post-progression health states are shown below (see Table 7).

Table 7. Utility values applied in the indirect treatment comparison for the subpopulation of patients who have received at least 2 previous treatments

Health state	Utility (SD)
Pre-progression, with treatment (PANO/BTZ/DEX)	0.679 (0.182)
Pre-progression, with treatment (LEN/DEX)	0.716 (0.201)
Pre-progression, no treatment	0.720* (0.200)
Post-progression	0.640 (0.128)
Dead	0
BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat; SD, standard deviation *Taken from Acaster et al.	

Cost and healthcare resource use

5.12 Five cost components were used in the model:

- Drug acquisition costs (from British National Formulary)
- Drug administration costs
- Treatment monitoring cost
- Costs for management of adverse events
- Terminal care costs

5.13 The average cost per cycle for panobinostat plus bortezomib and dexamethasone was calculated based on the mean dose intensity in PANORAMA-1. The total panobinostat cost per 3 week cycle was £[redacted] in the first treatment phase (cycle 1 to 8) and £[redacted] in the second treatment phase (cycle 9 to 16) for panobinostat plus bortezomib and dexamethasone. The cost of drug administration was included for bortezomib and it was assumed that it was administered intravenously. A scenario analysis was performed for subcutaneous use.

5.14 The cost of lenalidomide applied in the model was calculated as a weighted average of daily doses across all patient days in the MM-010 study. The resulting weighted average 28 days cycle cost for lenalidomide was £3,773 and transformed into a 3-weekly cycle cost of £2,830. Because the manufacturer of lenalidomide has agreed a patient access scheme (PAS), in which the cost of lenalidomide for people who remain on treatment for more than 26 cycles (each of 28 days) is met by the manufacturer, in the model lenalidomide costs were only applied for 35 (equating to approximately 26 x 28/21) 3-weekly cycles. The cost for dexamethasone was £2.59 per 28-day cycle (£1.94 per 3-weekly cycle).

5.15 The company also provided a summary of predicted resource use by category of cost using the 'Unadjusted Cox' method and deriving hazard ratios for the subgroup of patients who had received at least 2 previous treatments. These are detailed in Table 8 below, not including the PAS:

Table 8. Summary of predicted resource use by category of cost using the 'Unadjusted Cox' method and intravenous bortezomib and deriving hazard ratios for subgroup – discounted. Not including PAS. (Taken from CS, appendix 17, Table 34, page 60)

Item	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Drug costs	£46,381	£40,724	£5,657	£5,657	5656.95
Tests and monitoring (on treatment)	£2,882	£4,878	–£1,997	£1,997	1996.788
Tests and monitoring (No treatment)	£762	£97	£664	£664	664.1771
Last line of treatment	[redacted]	£100,598	[redacted]	[redacted]	[redacted]
Adverse events	£1,155	£191	£963	£963	963.3237
Terminal care	£1,139	£1,143	-£4	£4	4.323211
Total	[redacted]	£147,632	[redacted]	[redacted]	100%

ERG comments

5.16 The ERG considered the use of parametric curves fitted to the Kaplan-Meier data as appropriate to extrapolate beyond the trial time horizon and particularly the use of logistic regression because it is appropriate for binary responses i.e. progressed or not progressed. The ERG considered the use of the Gompertz curve was appropriate for the subgroup of interest because it implies an increasing mortality risk and is the most conservative model tested. However the ERG noted that the lenalidomide plus dexamethasone overall survival curve had not been compared to the underlying trial data.

5.17 The ERG also considered that the hazard ratios for progression-free survival and overall survival were calculated using 2 methods of indirect comparisons; Unadjusted Cox regression and matching adjusted indirect treatment comparison (MAIC). For the Unadjusted Cox regression the proportional hazards assumption is not consistent with the shape of the Kaplan-Meier curves for progression-free survival or overall survival for patients receiving either treatment. The curves cross suggesting that hazard ratios are likely to be an invalid method of relative effectiveness. The ERG therefore considers that the MAIC approach represents a potentially valid method of obtaining point estimates of relative effectiveness. However, after making the adjustments to the PANORAMA-1 trial data required by the MAIC method, the effective sample sizes were reduced from 314 to 137 in the full trial sample analysis therefore the MAIC estimates are also likely to be unreliable and biased by unobserved confounding.

5.18 The ERG was concerned that the utility of lenalidomide plus dexamethasone in the pre-progression health state was assumed to be the utility for bortezomib plus dexamethasone in the subgroup population.

5.19 The ERG was generally happy with the costs and resources used in the model but was unable to verify a number of the adverse events costs

included in the company's model. The company included a cost for lymphopenia but the clinical experts advising the ERG had suggested that the cost of lymphopenia should be 0. The ERG's clinical experts commented that tests would normally be administered no more than every 6 months and not every cycle as in the company's model.

5.20 The ERG noted that the adverse events occurrence was not well explained by the company and that the numbers in the PANORAMA-1 trial and those in the company's submission did not add up. The ERG clinical experts confirmed that the safety profile of panobinostat was a realistic description and corresponds to literature for panobinostat and other deactylase inhibitors.

5.21 The ERG was unclear why the decrement in utilities associated with the adverse events was not taken into account in the model. The company did not include any explanation for this. The ERG had concerns about this omission because of the differences in the safety profiles between panobinostat and the comparator treatments.

Company's base-case results and sensitivity analysis

5.22 The company considered that the 'Unadjusted Cox' method on the subpopulation of people who had received treatment with at least 2 previous lines of treatment was the most appropriate approaches for deriving the relative efficacies of the panobinostat plus bortezomib and dexamethasone compared with lenalidomide plus dexamethasone. The base case results are shown in Table 9 and include both intravenous administration and subcutaneous administration of bortezomib.

Table 9. Company's base case ICERs including PAS calculated using the unadjusted Cox method for the subgroup of patients who had received at least 2 previous treatments. (Taken from PAS submission template, Table 4 pages 17 and 18)

a) Intravenous BTZ administration assumed and PAS included

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
PAN/BTZ/DEX	£150,989	1.521	£3,357	0.0518	£64,819
LEN/DEX	£147,632	1.469			
QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; BTZ: bortezomib ; PAN : panobinostat ; DEX : dexamethasone ; LEN : lenalidomide					

b) Subcutaneous BTZ administration assumed and PAS included:

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
PAN/BTZ/DEX	£147,308	1.521	-£324	0.0518	dominant
LEN/DEX	£147,632	1.469			
QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; BTZ: bortezomib ; PAN : panobinostat ; DEX : dexamethasone ; LEN : lenalidomide Dominant means that the intervention is less expensive and more effective than treatment with the comparator.					

5.23 The company considered that the model underestimated the clinical value of panobinostat by underestimating the median progression-free survival by 0.5 months and the median overall survival by 4.3 months. However, the model overestimated the median treatment duration, hence the cost associated with panobinostat plus bortezomib and dexamethasone treatment (see Table 10).

Table 10. Summary of model results compared with clinical data (taken from CS, appendix 17, Table 28, page 57).

Outcome	Clinical trial result (Prior IMiD, BTZ and ≥ 2 LoT)	Model result
Median PFS (PANO/BTZ/DEX)	12.5 months	12.0 months
Median OS (PANO/BTZ/DEX)	[redacted] months	26.2 months
Median treatment duration (PANO/BTZ/DEX)	4.2 months	5.5 months
Abbreviations: BRT, bortezomib; DEX, dexamethasone; OS, overall survival; PANO, panobinostat; PFS, progression-free survival.		

ERG comments

5.24 The ERG noted that the small differences in QALYs between the panobinostat treatment group and the comparator lenalidomide group made the results difficult to interpret. The company did not provide the results of the deterministic sensitivity on the ICER.

Company sensitivity analyses

5.25 The company presented 3 tornado diagrams showing the uncertainty in the incremental QALYs, incremental costs, and ICERs for the 15 most sensitive model parameters are demonstrated in the tornado diagram (see company's PAS template pages 19 and 20). These demonstrated that the model outcomes (such as QALYs and costs) were sensitive to the hazard ratio estimating lenalidomide plus dexamethasone relative efficacy (for progression-free survival and overall survival).

Company scenarios

5.26 Scenario analyses were conducted around assumptions in the model (see Table 11).

Table 11. Scenario analyses conducted with base values and scenario values (taken from CS, appendix 17, Table 35, page 63)

Parameter	Base Value	Scenario Value
Discount rate	3.5%	5%
Time Horizon	25 years	5 years
		10 years
Overall survival	Gompertz	Weibull
		Kaplan–Meier + best fitting model
Progression-free survival	Weibull	Gompertz
Time to discontinuation	Fitted curve	Kaplan–Meier estimates
Distribution of post-progression treatments		a) Equal to the full PANORAMA-1 population
		b) Equal to prior IMiD population of the PANORAMA-1 trial
Utility associated with LEN/DEX	Equal to BTZ/DEX	Equal to off-treatment interval
Methodology generating HRs for LEN/DEX versus PANO/BTZ/DEX	'Unadjusted Cox' (2 to 3 prior lines of treatment)	'Naïve' (ITT)
		'Unadjusted Cox' (ITT)
		'MAIC' (ITT)
		'Naïve' (2 to 3 prior lines of treatment)
Threshold analyses	-	Various HR of PFS and price scenarios

5.27 When the company discounted the costs, altered the time horizon of the model to be either 5 or 10 years, used a Gompertz parametric curve to calculate the hazard ratio for progression-free survival, used the trial data to calculate the risk of discontinuation of treatment, when the post-progression treatment is based on the full trial population or only those with previous immunomodulatory treatment, assuming lenalidomide plus dexamethasone has no utility decrement, that the matching adjusted indirect treatment comparison is used for the intention to treat population or that the hazard ratios are 1.1 or 1.2 the ICER for panobinostat plus bortezomib and dexamethasone compared with bortezomib plus

dexamethasone was dominant (the intervention was less expensive and more effective than the comparator).

5.28 If the overall survival data is fitted with a Weibull parametric curve the ICER including the PAS is £32,200 per QALY gained for panobinostat plus bortezomib and dexamethasone compared with bortezomib plus dexamethasone. If the hazard ratio for progression-free survival was presumed to be between 0.8 and 1 the ICER including the PAS ranged from £223,800 to £24,700 per QALY gained respectively. If the Unadjusted Cox or naïve methods were applied to calculate the hazard ratios for progression-free survival or overall survival the ICER including the PAS was £223, 600 and £341,900 per QALY gained respectively.

ERG comments

5.29 The ERG determined that the model outcomes (i.e. QALYs and costs) were most sensitive to the hazards for progression-free survival and overall survival. However, the results presented in the Tornado diagrams showed the progression-free survival hazard ratio for lenalidomide plus dexamethasone twice.

5.30 The ERG also noted that the company considered the model results to be more sensitive to the cost of the panobinostat plus bortezomib and dexamethasone treatment. However this parameter has not been varied in the deterministic sensitivity analysis therefore the ERG is not clear on the basis of this statement.

5.31 The ERG was unsure why the company did not use the common comparators method to analyse the subgroup because the company did not provide an explanation for this. There was also no explanation provided for using the matching adjusted indirect treatment comparison (MAIC) method for the full population and the Unadjusted Cox method for the subgroup. The ERG also noted that the result of the MAIC and Unadjusted Cox methods showed only a small incremental QALY gain of

0.0295 and 0.0518 respectively making it difficult to determine the reliability of the results.

ERG exploratory analyses

5.32 As a result of the timing of the approval of the PAS submitted by the company, the ERG's exploratory analyses including the PAS discount is not included here and will be provided in a separate document.

Innovation

5.33 Justifications for considering panobinostat to be innovative:

- Two of the patient and carer groups considered panobinostat to be innovative because it uses a different treatment pathway (blocking the action of histone deacetylase in myeloma cells) to currently available multiple myeloma treatments.

5.34 Justification for not considering panobinostat to be innovative:

- The company considers panobinostat to be innovative because of its novel inhibition of the proteasome and aggresome pathways.

6 End-of-life considerations

6.1 The company provided end-of-life data for the full trial population but not the subgroup of patients who had received at least 2 previous treatments.

Table 12 End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Data from the Haematological Malignancy Research Network in relation to a cohort of 1645 MM patients diagnosed between September 2004 and August 2011, reported that a median OS was 1.2 years from the start of second-line treatment, and 1.4 years when the second-line treatment was a bortezomib-based regimen
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	OS data from the PANORAMA-1 trial are not yet mature but the most recent analysis, reported a median OS of 38.24 months for the PANO/BTZ/DEX group and 35.38 months for the PBO/BTZ/DEX group, corresponding to 2.86 months (p = 0.1783)
The treatment is licensed or otherwise indicated for small patient populations	Approximately 1300 patients in England and Wales would be eligible to receive panobinostat annually

7 Equality issues

7.1 No equalities issues were raised during the scoping process or by consultees and commentators.

8 Authors

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with input from the Lead Team (David Black, Robert Walton and Judith Wardle).

Appendix A: Clinical efficacy section of the draft European public assessment report

The positive CHMP opinion can be found at the link below:

http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/003725/WC500188792.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Panobinostat for treating multiple myeloma in people who have received at least 1 prior therapy

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of panobinostat within its marketing authorisation for treating multiple myeloma in people who have received at least 1 prior therapy.

Background

Multiple myeloma is a form of cancer that arises from plasma cells (a type of white blood cell) in the bone marrow. Myeloma cells produce large quantities of an abnormal antibody, known as paraprotein. Unlike normal antibodies, paraprotein has no useful function and lacks the capacity to fight infection. Myeloma cells supress the development of normal blood cells that are responsible for fighting infection (white blood cells), carrying oxygen around the body (red blood cells) and blood clotting (platelets). The term multiple myeloma refers to the presence of more than one site of affected bone at the time of diagnosis. People with multiple myeloma can experience bone pain, bone fractures, tiredness (due to anaemia), infections, hypercalcaemia (too much calcium in the blood) and kidney problems.

In 2011, 4039 people were diagnosed with multiple myeloma in England. It is most frequently diagnosed in older people, with 43% of people diagnosed aged 75 years and over. Multiple myeloma is more common in men than in women and the incidence is also reported to be higher in people of African and Caribbean family origin. There were 2303 deaths in England in 2012. The 5-year survival rate for adults with multiple myeloma in England is estimated to be 37.1%.

Multiple myeloma is an incurable disease. The main aims of therapy are to prolong survival and maintain a good quality of life by controlling the disease and relieving symptoms. Following initial treatment, subsequent therapy is influenced by previous treatment and response to it, duration of remission, comorbidities and patient preference. NICE technology appraisal guidance 129 recommends bortezomib monotherapy as an option for treating progressive multiple myeloma in people who are at first relapse having received 1 prior therapy and who have undergone, or are unsuitable for bone marrow transplantation. NICE technology appraisal guidance 171 also recommends lenalidomide in combination with dexamethasone as a treatment option for people with multiple myeloma who have received at least 2 prior therapies. Other subsequent treatment options may include repeating high-

dose chemotherapy or chemotherapy with alkylating agents and anthracyclines, thalidomide and corticosteroids.

The technology

Panobinostat (Farydak, Novartis Pharmaceuticals UK) is an oral potent histone deacetylase inhibitor that disrupts a key mechanism in the transformation of normal cells to cancerous cells and selectively targets tumour cells for cell death.

Panobinostat does not currently have a marketing authorisation in the UK for multiple myeloma that has been previously treated with at least 1 prior therapy. Panobinostat has been studied in combination with bortezomib and dexamethasone compared with bortezomib and dexamethasone in adults with relapsed disease, and in adults with relapsed and refractory multiple myeloma who have received at least 1 prior therapy.

Intervention(s)	Panobinostat in combination with bortezomib and dexamethasone
Population(s)	People with multiple myeloma who have received at least 1 prior therapy
Comparators	After 1 prior therapy: • Bortezomib monotherapy • Bortezomib plus dexamethasone After 2 or more prior therapies: • Bortezomib plus dexamethasone • Lenalidomide plus dexamethasone • Combination chemotherapy regimens with, for example, mephalan and doxorubicin, thalidomide and corticosteroids
Outcomes	The outcome measures to be considered include: • progression-free survival • overall survival • response rates • time to next treatment • adverse effects of treatment • health-related quality of life

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. Where comparator technologies are available through the Cancer Drugs Fund, the cost incurred by the Cancer Drugs Fund should be used in any economic analyses, rather than the list price.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. If the evidence allows, subgroup analyses based on number of lines of previous therapy will be considered.
Related NICE recommendations and NICE pathways	Related Technology Appraisals: Technology Appraisal No. 129, October 2007, 'Bortezomib monotherapy for relapsed multiple myeloma'. Guidance on Static list. Technology Appraisal No. 171, June 2009, 'Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy'. Guidance on Static list. Technology Appraisal No. 228, July 2011, 'Bortezomib and thalidomide for the first-line treatment of multiple myeloma'. Review proposal date July 2014. Technology Appraisal No. 311, April 2014, 'Bortezomib for induction therapy in multiple myeloma before high dose chemotherapy and autologous stem cell transplantation'. Review proposal date April 2017. Technology Appraisal in Preparation, 'Lenalidomide for the treatment of multiple myeloma following treatment with bortezomib' (part review of Technology Appraisal

	guidance 171). Earliest anticipated date of publication TBC. Technology Appraisal in Preparation, 'Pomalidomide for treating relapsed and refractory multiple myeloma previously treated with both lenalidomide and bortezomib'. Earliest anticipated date of publication TBC. Related Guidelines: Clinical Guideline in Preparation, 'Multiple myeloma: diagnosis and management of multiple myeloma'. Earliest anticipated date of publication January 2016. Cancer Service Guidance, October 2003, 'Improving Outcomes in Haematological Cancer'. NICE pathway: Multiple myeloma, Pathway created: December 2013 http://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers#path=view%3A/pathways/blood-and-bone-marrow-cancers/multiple-myeloma.xml&content=close
Related National Policy	National service framework: 'Improving outcomes: a strategy for cancer', January 2011. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/135516/dh_123394.pdf.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Panobinostat for treating multiple myeloma in people who have received at least 1 prior therapy

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Novartis Pharmaceuticals (panobinostat) Patient/carer group • Afiya Trust • Black Health Agency • Cancer Black Care • Cancer Equality • Cancer52 • Equalities National Council • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Leukaemia Cancer Society • Leukaemia CARE • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • Muslim Health Network • Myeloma UK • Rarer Cancers Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Professional groups • Association of Cancer Physicians • British Committee for Standards in Haematology • British Society for Haematology • British Geriatrics Society • British Psychosocial Oncology Society • Cancer Research UK	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Commissioning Support Appraisals Service • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator Companies • Accord Healthcare (doxorubicin) • Actavis (doxorubicin) • Aspen (melphalan) • Baxter (cyclophosphamide) • Celgene (lenalidomide, thalidomide) • Hameln Pharmaceuticals (dexamethasone) • Hospira (dexamethasone, vincristine) • Janssen (bortezomib, doxorubicin) • Medac GmbH (doxorubicin) • Merck Sharp & Dohme (dexamethasone) • Pfizer (cyclophosphamide, doxorubicin) • Rosemont Pharmaceuticals

Consultees	**Commentators (no right to submit or appeal)**
• Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • UK Health Forum • UK Myeloma Forum • United Kingdom Clinical Pharmacy Association • United Kingdom Oncology Nursing Society <u>Others</u> • Department of Health • NHS Bexley CCG • NHS England • NHS Scarborough and Ryedale CCG • Welsh Government	(dexamethasone) • Teva UK (vincristine) <u>Relevant research groups</u> • Clinical Trials Research Unit (CTRU), University of Leeds • Cochrane Haematological Malignancies Group • Elimination of Leukaemia Fund • Health Research Authority • Leukaemia and Lymphoma Research • Leukaemia Busters • Leuka • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research • Research Institute for the Care of Older People • The Institute of Cancer Research <u>Evidence Review Group</u> • Peninsula Technology Assesment Group, University of Exeter (PenTAG)National Institute for Health Research Health Technology Assessment Programme <u>Associated Guideline Groups</u> • National Collaborating Centre for Cancer <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales NHS Trust

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do share it. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non- company consultees are invited to submit a statement, respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies;
Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the company evidence submission to the Institute.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy (ID663)

Company evidence submission

2015

File name	Version	Contains confidential information	Date
		Yes/no	**20 May 2015**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

Tables

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Abbreviations

AIC	Akaike information criterion
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplantation
ASH	American Society of Hematology
BCSH	British Committee for Standards in Haematology
BIC	Bayesian information criterion
BNF	British National Formulary
BTZ	bortezomib
CF	Cognitive Functioning
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CR	complete response
CSR	Clinical Study Report
CTD	cyclophosphamide, thalidomide and dexamethasone
DAC	deacetylases
DEX	dexamethasone
DOX	doxorubicin
EBMT	European Group for Blood and Bone Marrow Transplant
ECG,	electrocardiogram
EF	Emotional Functioning
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	5-dimension EuroQol questionnaire
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
GHS	Global Health Status
GOG	Gynecologic Oncology Group
HDAC	histone deacetylase
HERC	Health Economics Research Centre
HMRN	Haematological Malignancy Research Network
HR	hazard ratio
HRQL	health-related quality of life
HSP	heat shock protein
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IQR	interquartile range

IRC	Independent Review Committee
LEN	lenalidomide
LLoT	last line of treatment
MAIC	matching adjusted indirect treatment comparison
mEBMT	modified European Group for Blood and Bone Marrow Transplant
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma
MR	minimal response
MRU	Medical Resource Utilisation
NCDF	National Cancer Drugs Fund
nCR	near-complete response
NICE	National Institute for Health and Care Excellence
Ntx	Neurotoxicity
ODAC	Oncologic Drugs Advisory Committee
ORR	overall/objective response rate
OS	overall survival
PANO	panobinostat
PANORAMA	PANobinostat ORAl in multiple MyelomA
PAS	Patient Access Scheme
PBO	placebo
PF	Physical Functioning
PFS	progression-free survival
PI	proteasome inhibitor
POM	pomalidomide
PR	partial response
QALY	quality-adjusted life years
QLQ-C30	Quality of Life Questionnaire-core 30
QLQ-MY20	EORTC MM-specific module
QTcF	QT interval corrected for heart rate by use of Fridericia's QT formula
RCT	randomised controlled trial
RF	Role Functioning
rrMM	relapsed/refractory MM
SD	standard deviation
SF	Social Functioning
SMC	Scottish Medicines Consortium
STA	Single Technology Appraisal
TA	Technology Appraisal
TFI	treatment-free interval
THAL	thalidomide
TTP	time to progression

VBA	Visual Basic for Applications
VGPR	very good partial response

1 Executive summary

1.1 Statement of decision problem

Table 1 summarises the decision problem relating to this submission.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with multiple myeloma who have received at least 1 prior therapy	People with multiple myeloma who have received at least 1 prior therapy	
Intervention	Panobinostat in combination with bortezomib and dexamethasone	Panobinostat in combination with bortezomib and dexamethasone	
Comparator (s)	After 1 prior therapy: • Bortezomib monotherapy • Bortezomib plus dexamethasone After 2 or more prior therapies: • Bortezomib plus dexamethasone • Lenalidomide plus dexamethasone • Combination chemotherapy regimens with, for example, mephalan and doxorubicin, thalidomide and corticosteroids	After 1 prior therapy: • Bortezomib plus dexamethasone After 2 or more prior therapies including an IMID and BTZ: • Lenalidomide plus dexamethasone	There are insufficient robust data to compare panobinostat/bortezomib/dexamethasone with other regimens, and the chosen comparators are the most relevant for current clinical practice in England and Wales Bortezomib in combination with dexamethasone is not available in the UK after prior bortezomib.
Outcomes	The outcome measures to be considered include: • progression-free survival • overall survival • response rates • time to next treatment • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • progression-free survival • overall survival • response rates • treatment-free interval • adverse effects of treatment • health-related quality of life	Treatment-free interval, the time period between discontinuation of panobinostat/bortezomib/dexamethasone or the comparator bortezomib/dexamethasone and resuming therapy with the next line of therapy on disease progression provides an addition and highly relevant measure of the benefit of therapy to patients. During this period patients experience a better quality of life being off treatment and without progressive disease
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The		

	reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. Where comparator technologies are available through the Cancer Drugs Fund, the cost incurred by the Cancer Drugs Fund should be used in any economic analyses, rather than the list price.		
Subgroups to be considered	If the evidence allows, subgroup analyses based on number of lines of previous therapy will be considered.	Two subgroups, patients having received prior therapy with an immunomodulatory agent (IMiD) plus bortezomib, and patients having received prior therapy with an immunomodulatory agent (IMiD) plus bortezomib and at least two prior lines of therapy, are considered.	Rationale for considering the two subgroups. One of the most relevant factors regarding the choice of therapy for patients with rrMM is the mechanisms of action of the therapies patients have previously received. Proteasome inhibitors (PIs) and IMiDs are the two most active drugs currently used and patients failing after receiving both therapies have a poor outcome and few treatment options. Patients having received prior therapy with an IMiD plus bortezomib was a pre-defined subgroup included in the analysis of the pivotal PANORAMA-1 trial and hence is relevant to consider. In England and Wales, most patients receive bortezomib and IMiD therapy as separate lines of treatment, hence most patients who have failed both bortezomib and an IMiD have also received at least two prior lines of therapy. Thus this subgroup corresponds to the likely patient population who would

			receive panobinostat in England and Wales
Special considerations including issues related to equity or equality			

1.2 Description of the technology being appraised

Panobinostat is a novel pan-deacetylase (DAC) inhibitor with potent anti-tumour activity.[1] DACs (also known as histone deacetylases) are nuclear and/or cytoplasmic enzymes that specifically remove acetyl groups from target proteins such as histones, and are believed to be involved in the epigenetic regulation of cells.[1-4] Dysregulated DAC activity is a common finding in cancer cells, including multiple myeloma (MM). Panobinostat is the most potent pan-DAC inhibitor developed to date. Through its effects on histone acetylation and gene expression, as well as on the oncogenic function of non-histone proteins such as HSP90, panobinostat offers a multifaceted approach to inhibit proliferation and survival of MM cells. Myeloma cells overproduce misfolded proteins and are heavily reliant on three pathways for the clearance of such proteins and hence for cell survival. Panobinostat has been shown to act synergistically with the proteasome inhibitor (PI), bortezomib, resulting in the inhibition of all three of these pathways, thereby inducing apoptosis. Combining panobinostat with bortezomib therefore represents a rational approach to improving outcomes in the management of MM, as has been borne out in the clinic.[5,6, 7,8]

As summarised in Table 2, in line with the pivotal trial, the anticipated indication for panobinostat in the UK is: Panobinostat in combination with bortezomib and dexamethasone is indicated for the treatment of patients with MM who have received at least one prior therapy. Panobinostat is administered orally once a day and is given in conjunction with bortezomib and dexamethasone with therapy being given for two weeks followed by one week off therapy. Patients should be treated initially for eight 3-week cycles. It is recommended that patients with clinical benefit continue the treatment for four additional cycles each lasting 6 week.

Table 2 Technology being appraised

UK approved name and brand name	• Approved name: panobinostat • Brand name: Farydak®
Marketing authorisation/CE mark status	Panobinostat does not currently have UK marketing authorisation. A marketing authorisation application for panobinostat, in combination with bortezomib and dexamethasone, for the treatment of patients with MM who have received at least one prior therapy was submitted to the EMA in May 2014. An opinion from the Committee for Medicinal Products for Human Use (CHMP) is anticipated in May/June 2015, and the EMA approval is anticipated to be granted in August 2015.
Indications and any restriction(s) as described in the summary of product characteristics	The anticipated indication for panobinostat in the UK is: Panobinostat in combination with bortezomib and dexamethasone is indicated for the treatment of patients with MM who have received at least one prior therapy
Method of administration and dosage	Oral The recommended starting dose of panobinostat is 20 mg, taken orally once a day, on days 1, 3, 5, 8, 10

	and 12 of a 21-day (3-week) cycle. Patients should be treated initially for 8 cycles. It is recommended that patients with clinical benefit continue the treatment for four additional cycles each 6 weeks long

CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; MM, multiple myeloma

1.3 Summary of the clinical effectiveness analysis

Panobinostat is an innovative technology that has the potential to improve the outlook for patients with relapsed or relapsed and refractory MM (rrMM). The efficacy and safety of panobinostat in patients with rrMM has been demonstrated conclusively in the international multicentre pivotal trial, PANORAMA-1.[9] This double-blind placebo-controlled phase 3 trial randomised 768 patients with rrMM who had received 1 to 3 prior therapies to receive panobinostat in combination with bortezomib (BTZ) and dexamethasone (DEX) or placebo in combination with BTZ/DEX and results have been reported for a median follow-up of 31 months. Further supportive evidence has been reported for a single-arm phase 2 trial, PANORAMA-2,[10] which also involved patients with rrMM but who were refractory to bortezomib, and a phase 1b trial[11] which established the dose and dosing schedule chosen for investigation in the phase 2 and phase 3 trials.

1.3.1 Efficacy demonstrated in PANORAMA-1

In the PANORAMA-1 study, panobinostat plus BTZ/DEX (PANO/BTZ/DEX) provided a clinically meaningful extension of progression-free survival (PFS) to 12 months (from 8.1 months, $p < 0.0001$) and reduced the risk of progression by 37% versus BTZ/DEX. This benefit was achieved regardless of patient baseline characteristics, whether patients had relapsed or relapsed and refractory disease, or the prior number or type of therapy, and was confirmed in all sensitivity analyses performed. Furthermore, the median PFS observed for BTZ/DEX was consistent with that previously reported for bortezomib in patients with rrMM.[12-15] The statistically and clinically significant 4-month prolongation in PFS achieved with panobinostat triplet therapy is particularly impressive in that most patients would have received prior therapy with the highly effective current standards of care − bortezomib, lenalidomide or thalidomide − and over half of patients had received two or three prior lines of therapy.

Panobinostat in combination with BTZ/DEX improved the quality of response to treatment, with 28% of patients achieving a complete response (CR) or near complete response (nCR) compared with 16% of patients receiving BTZ/DEX, and prolonged the duration of response.[9] This is of particular significance since achieving at least a partial response (PR) has been shown to be associated with improved PFS and overall survival (OS),[16,17] and indeed a landmark analysis of data from the PANORAMA-1 study revealed a statistically significant prolongation of PFS for patients achieving a nCR/CR with panobinostat plus BTZ/DEX compared with those achieving a PR.[18] Furthermore,

achieving a deeper quality of response [CR versus a very good PR (VGPR) or PR] has been shown to be associated with a longer treatment-free interval (TFI, ie, the period from completion or discontinuation of therapy to the resumption of therapy on disease progression) in patients receiving BTZ/DEX.[19]

Panobinostat triplet therapy extended the TFI by 3.6 months (from 3.9 months for BTZ/DEX to 7.5 months for PANO/BTZ/DEX) in the overall population and by 4.5 months in patients achieving a CR/nCR. This is in contrast to the situation with the current standards of care (other than following autologous stem cell transplantation, ASCT) where the duration of the TFI achieved can be limited. Furthermore, the duration of exposure to BTZ/DEX and the associated PFS in the control group were consistent with those seen in previous studies[12,13,20,21,22] suggesting that the improved TFI associated with panobinostat is a true reflection of the treatment benefit provided by panobinostat rather than an anomaly of the PANORAMA-1 trial.

The prolonged TFI observed with panobinostat triplet therapy is expected to have a significant impact on health-related quality of life (HRQL) given that patients are likely to be free from symptoms and from the adverse events associated with treatment during the TFI. Indeed a survey of UK patients with MM found that prolongation of the TFI was associated with significant improvements in specific aspects of HRQL and that HRQL was greatest for patients in the first TFI compared with during active treatment.[23] The reported extension to the TFI is also consistent with an analysis of data from the pivotal phase 3 trial for bortezomib which reported a longer TFI in patients achieving a CR compared with those achieving a VGPR or PR;[19] thus the prolongation of TFI observed with panobinostat in PANORAMA-1 may well reflect the deeper responses achieved with PANO/BTZ/DEX over BTZ/DEX.

Survival data for the study are not yet mature enough to allow a final analysis, but interim OS data (as of 18 August 2014) show a numerical superiority for PANO/BTZ/DEX over BTZ/DEX (38.2 months versus 35.4 months).

1.3.2 Analysis of subgroups according to prior treatment

One of the most relevant factors regarding the choice of therapy for patients with rrMM is the mechanisms of action of the therapies patients have previously received. At present, the most active compounds used in MM are PIs and immunomodulatory drugs (IMiDs). Patients who fail after receiving both classes of drug generally have a poor outcome, thus underscoring the importance of introducing drugs with new mechanisms of action. In a further analysis of data from PANORAMA-1, the efficacy and safety of panobinostat triplet therapy was assessed in two subgroups of patients who had failed after receiving bortezomib and an IMiD − patients who had received prior therapy with an IMiD plus bortezomib (n = 193, 25% of the study population), and patients who had received prior IMiD plus bortezomib therapy and ≥ 2 prior lines of treatment (n = 147, 19% of the study population). In England and Wales, most patients receive an IMiD and bortezomib as separate lines of therapy.

Thus, in England and Wales most patients who have previously received therapy with an IMiD and bortezomib have received at least two prior lines of therapy and correspond to the latter subgroup.

Patients who had received prior IMiD plus bortezomib therapy were one of the pre-specified subgroups considered in the analysis of PANORAMA-1. The benefit achieved with PANO/BTZ/DEX over BTZ/DEX in this subgroup was greater than that observed in the overall study population. PFS was prolonged by a clinically meaningful 4.8 months (from 5.8 months to 10.6 months) with the addition of panobinostat to BTZ/DEX, demonstrating a 48% risk reduction in PFS in favour of treatment with PANO/BTZ/DEX (hazard ratio, HR, 0.52; 95% CI: 0.36 to 0.76; p = 0.0005). The addition of panobinostat to BTZ/DEX was also associated with a higher ORR (59% versus 41%) and CR/nCR (22% versus 9%), and a longer median duration of response (12.0 months versus 8.3 months) and TTP (12.3 months versus 6.1 months) compared with the control group. Although interim OS data for the overall population are still immature, median OS in the panobinostat group was numerically higher than in the control group ([redacted] months versus [redacted] months, Figure 24) in this patient subgroup at the last interim OS analysis.

Efficacy outcomes for the second subgroup − patients who had received prior IMiD plus bortezomib and ≥ 2 prior lines of treatment − demonstrate a comparable or even greater benefit (compared to the IMiD plus bortezomib subgroup) for the addition of panobinostat to BTZ/DEX. Median PFS was extended by 7.8 months, representing a 53% reduction in the risk of progression, and median OS was extended by [redacted] months (from [redacted] months to [redacted] months). Increases in the ORR and CR/nCR with PANO/BTZ/DEX over the control group were similar to those observed in the prior IMiD plus bortezomib subgroup.

1.3.3 Supporting efficacy evidence

The results from PANORAMA-1 are supported by those from the PANORAMA-2 study, which demonstrated the benefits of panobinostat triplet therapy in heavily pre-treated patients who were refractory to bortezomib (almost all patients had also received lenalidomide and two-thirds had received thalidomide).[10] Moreover, a further analysis of data from the PANORAMA-2 study showed that patients who achieved at least a PR on panobinostat therapy had an improved median PFS and OS over patients who did not.[24] In this study at least a PR was achieved in 35% of patients and median OS was 17.5 months. This compares favourably to the best ORR of 24% and median OS of 9 months reported in an observational study for a similar patient population (refractory to bortezomib and IMiDs) with a median of four prior therapies who received various therapies.[14] These results thus indicate that the panobinostat regimen can benefit patients refractory to both bortezomib and IMiDs, a patient population for whom there are very few effective options.

1.3.4 Safety profile

In both PANORAMA studies, panobinostat triplet therapy was generally well tolerated with a predictable and manageable safety profile. Diarrhoea, asthenia and fatigue were the most frequently reported non-haematological grade 3/4 adverse events associated with panobinostat triplet therapy in the PANORAMA-1 study. Diarrhoea was managed by dose adjustment or interruption and anti-diarrhoeal medication, and few patients discontinued treatment owing to diarrhoea, asthenia or fatigue of any grade. Furthermore, panobinostat triplet therapy was not associated with an increased risk of grade 3/4 peripheral neuropathy versus BTZ/DEX. Thrombocytopenia was the most frequently reported grade 3/4 haematological adverse event associated with panobinostat triplet therapy, but was reversible, non-cumulative and rarely led to treatment discontinuation; furthermore, the rate of grade 3/4 haemorrhages was low (4%). Grade 3/4 neutropenia was reported in approximately one-third of patients who received panobinostat triplet therapy but febrile neutropenia was rare. Rates of discontinuation due to adverse events and the incidence of on-treatment deaths with PANO/BTZ/DEX were within the ranges reported for current standards of care, namely bortezomib-based, lenalidomide-based regimens, but were higher than in the BTZ/DEX group (36% versus 20%). Diarrhoea was the adverse event most frequently leading to discontinuation in the panobinostat group but lead to discontinuation in only 4.5% of patients. The safety profile observed in the PANORAMA-2 study was in general agreement with that reported for the PANORAMA-1 study, except for a noticeably lower incidence of grade 3/4 sepsis in both treatment groups in the PANORAMA-1 study, possibly reflecting better management of this adverse event in the phase 3 study.[25]

In both PANORAMA-1 studies, bortezomib was administered intravenously. In the UK (and in most countries), there is a tendency of bortezomib being administered subcutaneously following demonstration that the subcutaneous route is better tolerated and provides equivalent efficacy to intravenous administration. In particular, a phase 3 trial comparing intravenous and subcutaneous administration demonstrated a lower incidence of the following grade 3/4 adverse events of at least 5%: neuralgia (3% subcutaneous versus 9% intravenous), peripheral neuropathy (6% subcutaneous versus 15% intravenous), neutropenia (13% subcutaneous versus 18% intravenous) and thrombocytopenia (8% subcutaneous versus 16% intravenous).[26] A reduced frequency of intravenous administration of bortezomib has also been shown to improve tolerability, resulting in lower incidences of peripheral neuropathy, gastrointestinal toxicities and thrombocytopenia.[27] Consistent with this, a reduction in the incidence of new or worsening grade 3/4 adverse events was observed in PANORAMA-1 during the second treatment phase when bortezomib was administered once rather than twice weekly. These observations suggest that the incidence of grade 3/4 adverse events occurring with the panobinostat regimen in routine clinical practice is likely to be lower than that reported in the PANORAMA-1 study if bortezomib is administered subcutaneously, and that toxicities can be effectively managed by dose reductions.

When considering the two subgroups according to prior therapy (ie prior IMiD and bortezomib therapy, and prior IMiD and bortezomib and at least two lines of therapy), the safety profile of PANO/BTZ/DEX

was generally consistent with that in the overall population or slightly more favourable. In the control group, there was a higher rate of grade 3/4 thrombocytopenia (48%), and grade 3/4 infections (pneumonia: 14%; sepsis: 5%) in the subset of patients with having received prior IMiD and bortezomib therapy as compared to the subset of patients who had not received prior IMiD and bortezomib therapy, consistent with a more heavily-treated population and patients having more advanced disease. An analysis of the relative risk of experiencing adverse events in the panobinostat group versus the control group revealed a more favourable safety profile in patients who had previously received IMiD and bortezomib therapy compared with the total study population.

1.3.5 Conclusions

In conclusion, the results of the PANORAMA-1 pivotal trial, supported by those of the PANORAMA-2 trial, conclusively demonstrate the clinical benefits for the addition of panobinostat to BTZ/DEX in the management of rrMM, including in patients who were heavily pre-treated. These benefits included an extension of the time during which patients are treatment-free, which can be expected to translate into improvements in HRQL when considered over the entire period from initiating therapy with panobinostat plus BTZ/DEX or BTZ/DEX, until relapse and progression to the next line of therapy. Furthermore, a numerical increase in median OS has been observed although data are, as yet, immature. Panobinostat thus provides a valuable addition to the armamentarium for the management of rrMM and offers patients and their families the benefits of a meaningful prolongation of remission.

1.4 Summary of the cost-effectiveness analysis

Table 3 Incremental cost-effectiveness results via direct (a) and indirect (b) treatment comparison

a) Base case: assuming £776 per 20 mg capsule

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
PANO/BTZ/DEX	£197,922	3.570	2.404	£44,487	0.773	0.563	£79,025	£79,025
BTZ/DEX	£153,434	2.797	1.841					

BTZ, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PANO, panobinostat; QALYs, quality-adjusted life years

b) Base case: assuming £776 per 20 mg capsule

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per LYs gained[a]	ICER (£) Cost per QALYs gained[a]
'MAIC' deriving HRs from full trial populations	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.071	0.0295	£[redacted]	£[redacted]
	LEN/DEX	£148,567	2.216	1.491					
'Unadjusted Cox' deriving HRs from subpopulation (2 to 3 prior lines)	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.102	0.0518	£[redacted]	£[redacted]
	LEN/DEX	£147,632	2.186	1.469					

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LYG, life years gained; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; QALYs, quality-adjusted life years

2 The technology

2.1 Description of the technology

- Brand name: Farydak®
- Approved name: panobinostat
- Panobinostat, a hydroxamic acid derivative, is a potent class I, II and IV pan-deacetylase inhibitor with anti-tumour activity.
- Pharmacotherapeutic group: other antineoplastic agents, ATC code: L01XX42[28]

DAC inhibition is a recognised target for anti-myeloma therapies

Deacetylases (DAC, also known as histone deacetylases, HDAC) are nuclear and/or cytoplasmic enzymes that specifically remove acetyl groups from target proteins such as histones, and are believed to be involved in the epigenetic regulation of cells.[1-4] Dysregulated DAC activity is a common finding in cancer cells, including multiple myeloma (MM), and results in aberrant gene expression (notably decreased expression of tumour suppressor genes) and modulation of the activity of proteins implicated in tumourigenesis (for example, p53, α-tubulin and HSP90). DAC inhibitors thus have inhibitory effects in cancer cells. Specifically, in MM cells, DAC inhibition has been shown to upregulate the expression of the tumour suppressor gene, p21, leading to cell-cycle arrest followed by apoptosis; disrupt the signalling pathway between MM cells and bone marrow stromal cells; and inhibit the response to unfolded proteins (mediated through inhibition of the aggresomes protein degradation pathway) resulting in the build-up of abnormal proteins within the cell (as described below).[29,30]

Panobinostat is a potent pan-DAC inhibitor having potent anti-tumour activity

Panobinostat is a novel pan-DAC inhibitor with potent anti-tumour activity.[1] Panobinostat inhibits the activity of the majority of class I, IIa, IIb, and IV DAC isoforms at nanomolar concentrations. It is the most potent pan-DAC inhibitor developed to date and is thought to exert its cytotoxic effects through the induction of epigenetic changes that modify genome-wide gene-expression patterns, as well as via direct cytogenetic actions.[2,3] Thus, through its effects on histone acetylation and gene expression, as well as on the oncogenic function of non-histone proteins such as HSP90, panobinostat offers a multifaceted approach to inhibit proliferation and survival of MM cells.

In myeloma cells, panobinostat has been shown to inhibit the activity of two pathways essential for clearance of abnormal proteins and hence cell survival

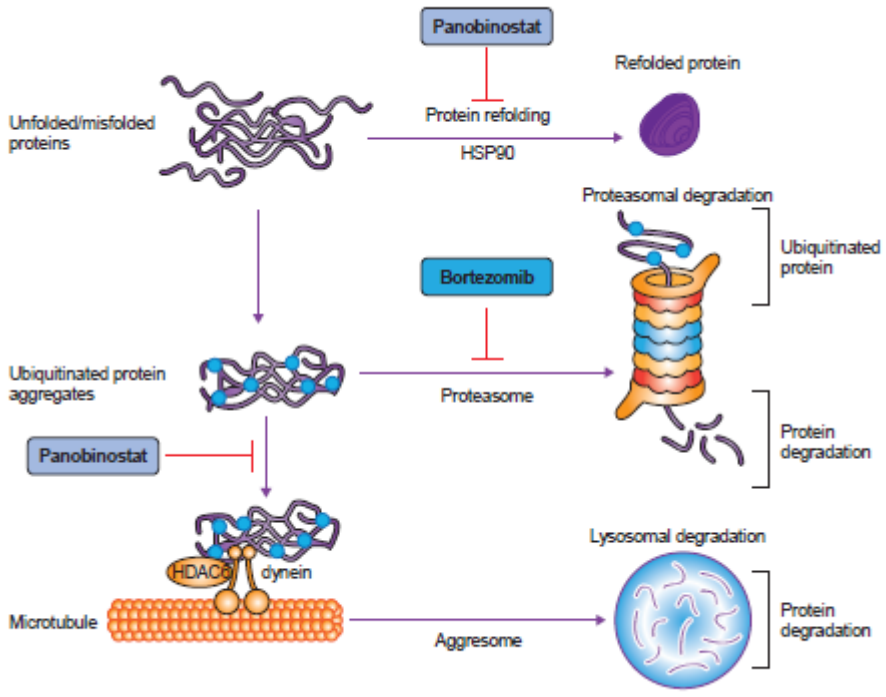
Myeloma cells overproduce misfolded proteins, particularly immunoglobulins, and are heavily reliant on three pathways for the clearance of such proteins and hence for cell survival. The proteasome and aggresome pathways are important for the degradation of misfolded proteins, while refolding of misfolded proteins occurs via the activity of the heat shock protein HSP90.

Panobinostat inhibits two of these pathways:[3,29,31]

- it leads to accumulation of acetylated HSP90 chaperone protein via inhibition of HDAC6, blocking protein refolding;[31]
- and it inhibits the binding of ubiquitinated misfolded proteins to HDAC6 and dynein, thereby preventing the formation of aggresomes and hence the degradation of proteins via the lysosomes (Figure 1).[32] The result is the accumulation of misfolded proteins, which leads to cell apoptosis.[3]

The third pathway involved in the clearance of abnormal proteins in MM is via the proteasome (Figure 1); inhibition of the proteasome arrests MM cell growth and triggers apoptosis through accumulation of misfolded proteins.[33] This pathway is the target of the proteasome inhibitors (PI) such as bortezomib (BTZ) which has emerged as an important therapeutic agent in the management of MM.[34]

Figure 1 Processing of paraproteins and the inhibitory roles of panobinostat and bortezomib.



HDAC, histone deacetylase; HSP90, heat shock protein 90.

Panobinostat plus bortezomib represents a rational combination to improve clinical outcomes for patients with MM

Panobinostat is effective as a single agent as demonstrated in multiple *in-vitro* and *ex-vivo* studies, including in cells known to be resistant to current standards of care. Furthermore, the combination of bortezomib and panobinostat has been shown to be synergistic in *in-vitro* and *in-vivo* models of MM.[8] This is believed to reflect the fact that, together, panobinostat and bortezomib inhibit all three of the pathways involved in processing of abnormal proteins, thereby leading to the accumulation of these proteins within the MM cells. This in turn induces apoptosis. Therefore, combining panobinostat with the proteasome inhibitor bortezomib represents a rational approach to improving outcomes in the management of MM, as has been borne out in the clinic.[5,6, 7,8]

2.2 Marketing authorisation/CE marking and health technology assessment

Panobinostat does not currently have UK marketing authorisation. The European Medicines Agency (EMA) granted panobinostat orphan status for the treatment of MM in 2012. A marketing authorisation application for panobinostat, in combination with bortezomib and dexamethasone (DEX), for the treatment of patients with MM who have received at least one prior therapy was submitted to the EMA in May 2014. Based on this submission date, an opinion from the Committee for Medicinal Products for Human Use (CHMP) is anticipated in May/June 2015, and the EMA approval is anticipated to be granted in August 2015.

In line with the pivotal trial, the anticipated indication for panobinostat in the UK is: Panobinostat in combination with bortezomib and dexamethasone is indicated for the treatment of patients with MM who have received at least one prior therapy. The base case economic analysis is therefore based on this assumption. Unless stated otherwise, data presented in the submission are for this population. However, in the event that the licence is more restricted, we have also presented the most likely sub-group as a scenario analysis, with full results available (in Appendix 4)

The major issues discussed by the regulatory organisation have related to product quality and to the clinical profile of panobinostat. The regulator has asked that quality information on the starting material should be redefined. There has been discussion relating to: the clinical significance of progression-free survival (PFS) outcomes and immature overall survival (OS) data; discussion of the need for additional efficacy data in bortezomib refractory patients; and discussion of the risk:benefit profile of panobinostat.

The anticipated launch for panobinostat for the treatment of relapsed/refractory MM (rrMM) is September 2015. Panobinostat received regulatory approval from the US Food and Drug Administration (FDA) on 24 February 2014 for use in combination with bortezomib and

dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior regimens, including bortezomib and an immunomodulatory (IMiD) agent.[35]

A health technology assessment for panobinostat in MM is planned to be submitted to the Scottish Medicines Consortium (SMC) in September 2015.

2.3 Administration and costs of the technology

Table 4 summarises details of the treatment with panobinostat including the anticipated duration of treatment and acquisition costs.

Table 4 Unit costs of technology being appraised.

	Response	**Source**
Pharmaceutical formulation	Hard gelatine capsules	SmPC[28]
Acquisition cost (excluding VAT)	20 mg caps price (GBP) £776 15 mg caps price (GBP) £582 10 mg caps price (GBP) £582	Indicative costs only; yet to be submitted to DH
Method of administration	Oral	SmPC[28]
Doses	Panobinostat 10 mg hard capsules Panobinostat 15 mg hard capsules Panobinostat 20 mg hard capsules	SmPC[28]
Dosing frequency	The recommended starting dose of panobinostat is 20 mg, taken orally once a day, on days 1, 3, 5, 8, 10 and 12 of a 21-day (3-week) cycle. Patients should be treated initially for 8 cycles. It is recommended that patients with clinical benefit continue the treatment for four additional cycles each 6 weeks long	SmPC[28]
Average length of a course of treatment	Median duration: 5.0 months Mean duration: 6.63 months	San Miguel et al 2014[9]
Average cost of a course of treatment	Please advise	
Anticipated average interval between courses of treatments	N/A	
Anticipated number of repeat courses of treatments	It is anticipated that panobinostat is given as a single course of up to 12 cycles (48 weeks) (see dosing frequency above)	SmPC[28]
Dose adjustments	Modification of the treatment dose and/or schedule may be required based on individual tolerability, or may be affected by the dose of any bortezomib therapy used in combination with panobinostat (temporary or permanent changes in	SmPC[28]

	bortezomib dose may affect dosing of panobinostat and panobinostat should not be given alone). If a dose reduction in panobinostat is required, the dose should be reduced by decrements of 5 mg. The dose should not be reduced below 10 mg daily and the same treatment schedule (3-week treatment cycle) should be maintained	
Anticipated care setting	Secondary care setting	SmPC[28]

DH, Department of Health; N/A, not applicable; SmPC, Summary of Product Characteristics.

2.4 Changes in service provision and management

No additional tests or investigations are needed for selection or for administration of panobinostat. Treatment will be given in a secondary care setting, as for current treatments for rrMM.

Panobinostat is an oral medication and requires no specific monitoring at the time of administration. The technology is anticipated to have similar resource use to that associated with currently available treatment options in rrMM. Monitoring is anticipated to include laboratory tests, bone marrow biopsy and aspirate and periodic skeletal survey (bone X-ray) (see section 5.5 for details of resource use included in the economic model and relevant sources).

No additional infrastructure will be required.

Panobinostat in combination with bortezomib and dexamethasone is indicated for the treatment of patients with MM who have received at least one prior therapy. Panobinostat will therefore be given in a regimen that includes administration of bortezomib and dexamethasone.

2.5 Innovation

Panobinostat is an innovative technology that has the potential to improve the outlook for patients with rrMM. Panobinostat targets processes specific to the survival of myeloma cells (see section 2.1) and has been shown to provide significant clinical benefits including prolongation of PFS, deepening the response to therapy, and extension of the treatment-free interval (TFI, ie the period between completing second-line therapy and initiating subsequent therapy on disease progression) which is expected to translate into health-related quality of life (HRQL) benefits (see sections 4.7 and 4.13). Furthermore, studies suggest that panobinostat may help overcome resistance to other agents including proteasome inhibitors and thus offer improved outcomes for patients refractory to existing treatment options (see sections 4.11 and 4.13).[10,36]

3 Health condition and position of the technology in the treatment pathway

3.1 Disease overview and pathogenesis

Multiple myeloma is an incurable disease of the bone marrow

Despite recent therapeutic advances, MM remains a primarily incurable disease.[37-39] MM is a haematological malignancy, caused by the uncontrolled proliferation of antibody (immunoglobulin)-producing plasma cells.[39-44] In MM, specific plasma cell clones in bone marrow transform into malignant cells. These cells 'ignore' the normal restrictions on expansion and multiply indefinitely in the bone marrow, crowding out and impeding the proliferation of other haematopoietic cells, adversely affecting the production of normal blood cells and causing bone damage. Furthermore, the plasma clones produce huge amounts of abnormal antibodies (monoclonal or M protein) that are defective and so are unable to combat infection, and their cumulative bulk can cause renal damage. An expanding bone marrow tumour mass, lytic bone lesions, anaemia, increasingly severe organ impairment, and the overproduction of defective antibodies leading to immunodeficiency contribute to the characteristic signs and symptoms of MM (see below).[37,39-44]

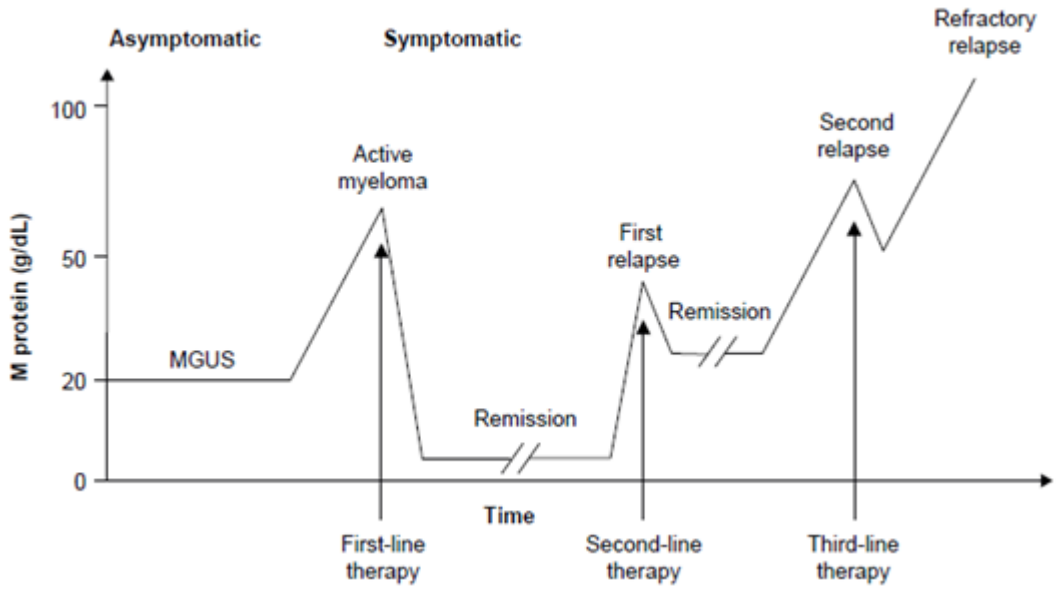
The pathogenesis of MM is complex and appears to involve a multistep process during which normal plasma cells transform into malignant myeloma cells. In almost all cases, MM is preceded by an indolent, premalignant, asymptomatic stage of disease called monoclonal gammopathy of undetermined significance (MGUS), which can progress to a smouldering myeloma and then to symptomatic MM.[37,39-45] Although it is not clear why some cases of MGUS progress to MM and others do not, both genetic and epigenetic factors are believed to contribute to the progression from normal plasma cells to MM cells.[2,3,38,44] During disease progression, changes and mutations in DNA sequences accumulate, along with and epigenetic events such as changes in DNA methylation, histone modification and RNA interference.[38,40,44] DACs play a key role in the modification of histones hence and influence pathways involved in gene expression, cell-cycle progression, DNA replication and repair and protein folding.[38] Epigenetic changes, such as histone deacetylation, appear to be events that facilitate disease progression beyond MGUS.[2,3,38,44] The bone microenvironment also contributes to pathogenesis.[37,41,44,45] The normal bone marrow supports a complex network of regulatory cell-signalling and developmental pathways. Myeloma cells subvert this homeostatic network to their own advantage, to support tumour-cell proliferation, survival and migration, in a manner that disrupts the normal balance between osteoclasts and osteoblasts. In late stages of the disease, tumour cells may spread to extramedullary locations such as the spleen, liver and extracellular spaces.[40]

Multiple myeloma is characterised by a pattern of remission and relapse and patients with rrMM have a poor prognosis

While most patients initially respond to first-line therapies, very few achieve long-term remission and the majority relapse and or become refractory to treatment, and require further lines of therapy.[39,46,47] The management of patients with rrMM remains a critically important area of patient care,[48] with an estimated 90% of patients becoming refractory to their first-line treatment or experiencing relapse within 10 years.[46]

The patient with rrMM has a poor prognosis, which worsens with increasing lines of therapy.[39,47,49] Patients with rrMM typically receive some form of salvage therapy (ie a regimen distinct from that received first-line) until relapse or toxicity and then go on to the next salvage option. However, the duration of plateau remission achieved becomes shorter and the incidence of relapse increases with increasing lines of therapy (Figure 2).[39] The pattern of shortened plateaus of remission and relapsing disease reflects the development of drug resistance, which eventually results in refractory disease. The duration of TFI between each therapy, associated with a better HRQL, also decreases with progressive lines of therapy.

Figure 2 Characteristic pattern of remission and relapse following conventional chemotherapy in multiple myeloma.



MGUS, monoclonal gammopathy of undetermined clinical significance.
Borello 2012.[39]

3.2 Effects of multiple myeloma on patients and carers

Multiple myeloma is typically associated with symptoms related to bone damage, hypercalcaemia, anaemia, renal dysfunction and compromised immune function

MM is typically associated with signs and symptoms related to bone damage, such as pain and or fracture, hypercalcaemia, anaemia, renal dysfunction and a propensity to infection.[43,50-52] These classic clinical manifestations and common symptoms of MM are often described by the acronym 'CRAB', which is typically observed together with compromised immune function.[43,53-55]

The 'C' in 'CRAB' stands for an elevation in blood calcium. Hypercalcaemia is associated with symptoms such as fatigue, thirst, nausea, vomiting, constipation, loss of appetite, drowsiness and confusion. The 'R' in 'CRAB' is for renal failure, which is caused by high levels of M protein and affects about 20% to 30% of patients with MM at diagnosis and as many as 50% of individuals at some point in the course of their disease. The 'A' refers to anaemia which is present in about 70% to 75% of patients at diagnosis, and the 'B' refers to bone damage, which in includes bone fracture, bone pain, osteoporosis and osteopenia, and spinal cord compression and paraplegia. Bone disease is present in about 60% of patients at diagnosis.[43,56] Patients with MM are often immunocompromised, owing to deficiencies in both humoral and cell-mediated immune function, and this manifests as a propensity for infection, particularly upper respiratory tract infection.[43] At diagnosis and during the course of the disease, as a result of the disease itself or as a side effect of treatments, many patients with MM experience peripheral neuropathy.[43,53,55]

In addition to the symptoms associated with MM, many patients have serious comorbidities. Patients are typically elderly, with about two-thirds aged 65 years or older, and prognosis is worse in older patients.[44,57-59] In the UK, based on a retrospective audit of 1645 patients performed by the Haematological Malignancy Research Network (HMRN), nearly 60% of patients are diagnosed at the age of 70 or later with the median age at diagnosis being 73.1 years (range, 33.4 to 95.5 years).[60] Many patients may have pre-existing or age-related comorbidities such as diabetes, cardiovascular disease, renal disease, pulmonary diseases and stroke, or comorbidities associated with MM such as fractures and renal impairment.[54,61,62] It has been reported that about three-quarters of elderly patients with MM have at least one comorbidity and almost one-fifth have three or more comorbidities.[61] The presence of comorbidities not only affects the patient's overall health status and prognosis[63] but also has an impact on treatment options, both in newly diagnosed patients and in those with relapsed or refractory disease.[57,59]

HRQL is significantly diminished in patients with MM relative to the general population and patients with other haematological malignancies

Cross-sectional studies have reported on HRQL in patients with MM according to International Staging System stage of disease, phase or type of treatment (ie first-line, second-line, chemotherapy, autologous stem cell transplantation (ASCT), etc) and symptom severity. Patients with newly

diagnosed MM have lower EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-core 30) scores, specifically the Global Health Status (GHS), Physical Functioning (PF) and Role Functioning (RF) scales, compared with those predicted for age-matched individuals from the general population. In a study comparing EORTC QLQ-C30 scores in 92 patients with newly diagnosed, untreated MM to age-matched controls, there were significant impairments in psychosocial quality of life dimensions. GHS score was 47.28 (control 70.63), PF score was 58.74 (control 80.75), RF score was 58.4 (control 87.04) and Emotional Functioning (EF) score was 66.67 (control 83.61).[64] Scores reported in further studies that included patients with more advanced MM and patients who had received several lines of treatment, also indicated a substantial impairment.[23,65-68] For example, a European, multicentre study involving 154 patients with MM (43% of whom had received at least one line of treatment) reported the following scores: GHS score was 60.1, PF score was 68.7 and Social Functioning (SF) score was 63.9.[67] A Danish study (n = 732) reported lower scores in patients with MM compared with other haematological malignancies: PF score was 66 (overall population, 77), RF score was 49 (overall population, 69), SF score was 72 (overall population, 82) and GHS score was 61 (overall population, 67).[66]

HRQL declines with increasing stage of disease and severity of symptoms

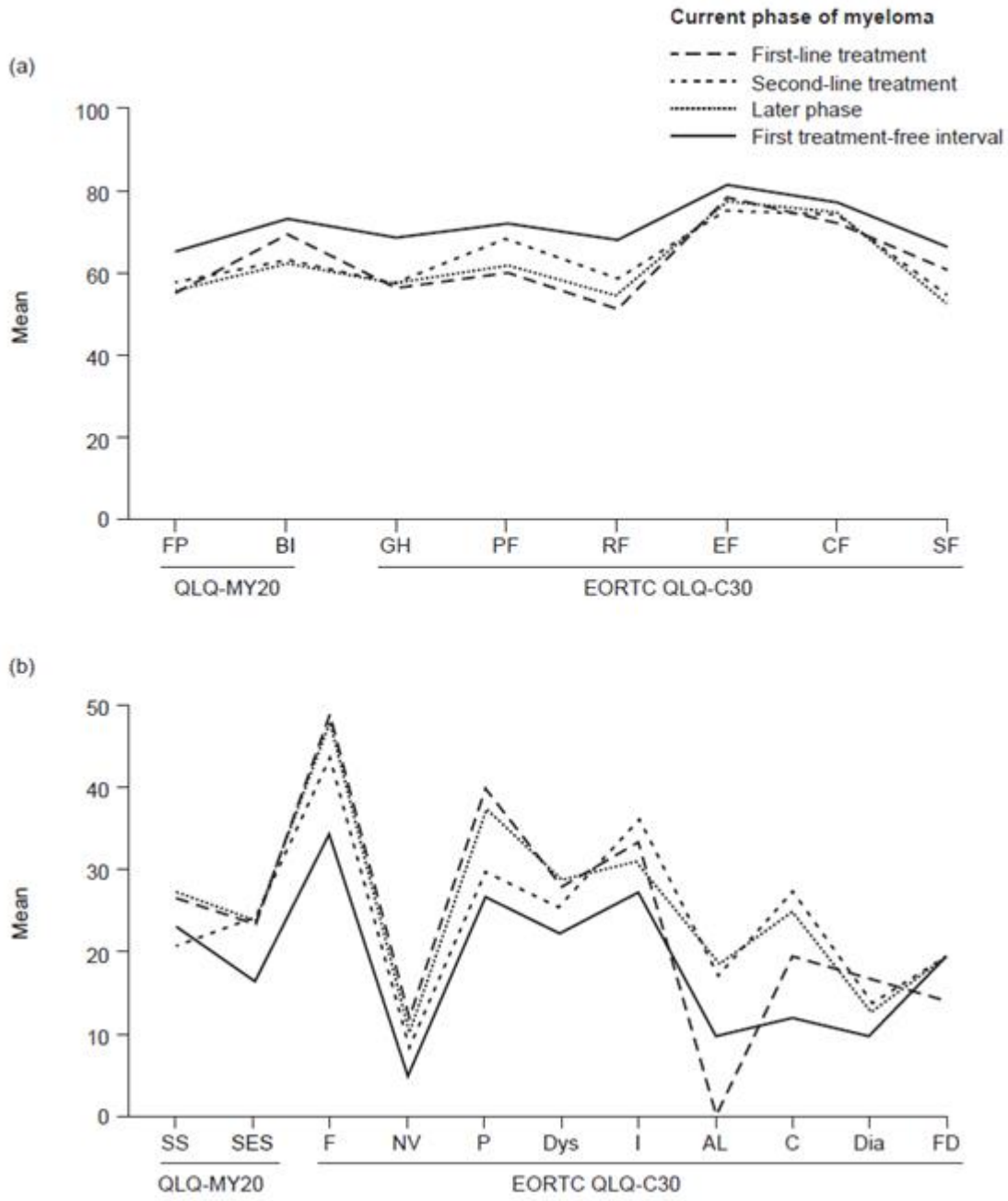
As MM advances and symptom severity increases, there is a marked decline in HRQL. For example, the European multicentre study (described above) involving 154 patients with MM used the EORTC QLQ-C30 and the EORTC Quality of Life Questionnaire multiple myeloma module (QLQ-MY20) tools to assess HRQL according to increasing severity of symptoms.[67] More than half of the patients in this study were on therapy and over 40% could be considered as having rrMM given their number of lines of previous therapy. Decreases in GHS, PF and SF were observed with increasing severity of symptoms; the mean GHS score was 79 for asymptomatic patients and decreased to 43 for patients with severe symptoms, and similar differences were see for PF (asymptomatic, 91; severe symptoms, 47) and SF (asymptomatic, 87; severe symptoms, 44).

HRQL improves for patients having a treatment-free interval following active treatment

A number of studies have shown that HRQL scores alter according to line of treatment and are improved at times when disease is in remission and patients are off treatment, ie during the TFI between lines of therapy. A UK survey of 605 patients with MM that studied the impact of TFI on HRQL, reported EORTC QLQ-C30, EORTC QLQ-MY20 and EQ-5D (5-dimension EuroQol questionnaire) scores to be indicative of better HRQL for patients during their first TFI compared with patients receiving active treatment (first or second line) or in later stages of disease.[23] For example, EQ-5D score was 0.63 for first-line treatment and increased to 0.72 for the first TFI but then decreased to 0.67 for second-line treatment and 0.63 for later stage disease. Scores for all functional domains were higher (indicative of better HRQL) and scores for all symptom score were lower (indicative of less severe symptoms) for patients during the TFI compared to during active treatment

(Figure 3). This study also reported that longer TFIs were significantly associated with improved HRQL on a range of domains including PF and RF as well as EQ-5D score. These data therefore suggest that therapies which allow patients to experience a treatment-free period offer significant HRQL benefits to patients and may argue for the use of regimens which are generally given for a limited period (eg bortezomib-based regimens) over those which are given continuously to disease progression (eg lenalidomide-based regimens).

Figure 3 Mean values for EORTC QLQ-C30 and QLQ-MY20 a) functional domains and b) symptom scores according to stage of treatment in patients with MM



EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – C30; EORTC QLQ-MY20, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module; AL, Appetite Loss; BI, Body Image; C, Constipation; CF, Cognitive Functioning; Dia, Diarrhoea; Dys, Dyspnea; EF, Emotional Functioning; F, Fatigue; FD, Financial Difficulties; FP, Future Perspective; GH, Global Health; I, Insomnia; NV, Nausea and Vomiting; P, Pain; PF, Physical Functioning; RF, Role Functioning; SES, Side Effects Score; SF, Social Functioning; SS, Disease Symptom Scale
Acaster et al, 2013[23]

The results of the UK survey are supported by those of an Italian study which assessed HRQL (using the EORTC QLQ-C30) for four disease phases − asymptomatic, symptomatic receiving ASCT, symptomatic receiving drug therapy and remission. GHS scores were found to be lowest for patients receiving drug therapy or ASCT (57.41 and 49.25, respectively) and to be similar for patients who were asymptomatic or in remission (71.05 and 72.02, respectively).[65]

Living with rrMM poses practical challenges for patients and their caregivers, impacting on daily function, productivity and well-being

Patients can be frustrated by the changes that MM brings in terms of affecting their activity and independence, and caregivers report being vulnerable to the high demands of caring for patients, as revealed by a UK study involving 20 patients with MM and 16 of their informal caregivers.[69] Furthermore, 35 to 40% of patients said that daily, family and social activities were limited. Another study (performed in Denmark) of patients with various haematological malignancies found that patients with MM often have difficulties with physical function, role function and social function,[66] and decrements in the domains of RF, PF, SF and Cognitive Function (CF) were also reported in a UK study involving 132 patients with MM.[68]

Work-life and productivity are affected for both patients and their caregivers as a result of disease.[69] Pain, one of the most frequent symptoms of MM, has been reported to affect day-to-day activities by 84% of patients with MM .[70] A total of 82% of patients reported that pain affected ability to work and 86% said pain affected their mobility.[70] Furthermore, a UK survey of 134 patients with MM reported that 27% of patients and 49% of partners had signs of clinical anxiety, whilst 25% of patients and 14% of partners had signs of clinical depression.[68]

3.3 Clinical pathway, current guidelines and the role of panobinostat

A number of practice guidelines and treatment recommendations, including those produced by the British Committee for Standards in Haematology (BCSH)[51] exist to support patient management. These all share a common goal for all patients with MM, namely to extend the length and quality of life by alleviating symptoms, controlling disease and minimising adverse effects of treatment and of disease.[51,52,71-74]

Few patients with newly-diagnosed MM achieve long-term remission; the majority develop rrMM and require further lines of therapy

While some patients may be eligible for ASCT,[46] only approximately 18% receive ASCT according to analysis of treatment outcomes for the HMRN cohort of 1543 patients;[60] thus this is not an option for all patients. Many people diagnosed with MM are not able to withstand intensive treatment such as high-dose chemotherapy with ASCT because of their age, other health problems or poor performance status.[52] For these patients with MM, current treatment options largely involve the use of two- to three-agent combination therapy. As described earlier (section 3.1), although most patients with MM initially respond to first-line therapies, very few achieve long-term remission and the majority relapse and require further lines of therapy.[39,46] In addition, approximately 25% to 35% of patients do not achieve a response to first-line therapy, adding to the number of patients who require therapy for rrMM.[46] For those with rrMM, the pattern of disease is one of remission and relapse and the use of increasing lines of therapy is associated with shorter durations of remission and a higher rate of relapse.[46,47]

The pathway of care relevant for panobinostat relates specifically to the treatment of patients with rrMM. Just as in newly diagnosed disease, the management goals for patients with rrMM focus on controlling disease, ameliorating symptoms, improving quality of life and extending survival.[51,75-78]

The British Committee for Standards in Haematology provides guidelines for management of rrMM

In the UK, the BCSH guidelines, published in 2014 by the British Society for Haematology and the UK Myeloma Forum, provide detailed recommendations for the management of rrMM.[51] These guidelines (which are in agreement with current National Institute for Health and Care Excellence (NICE) guidance – see section 3.5) note that treatment of patients with rrMM should be individualised, and state that it is not necessarily best practice to mandate particular therapies at specific stages of disease progression. Instead, treatment decisions should be made according to factors including: the timing of relapse; the efficacy and toxicity of drugs used in prior therapy; age; bone marrow and renal function; comorbidities; and patient preference.[51] The BCSH guidelines also consider that there is no consensus on the optimal treatment for high-risk patients and no evidence to date that genetic testing should inform treatment choices.

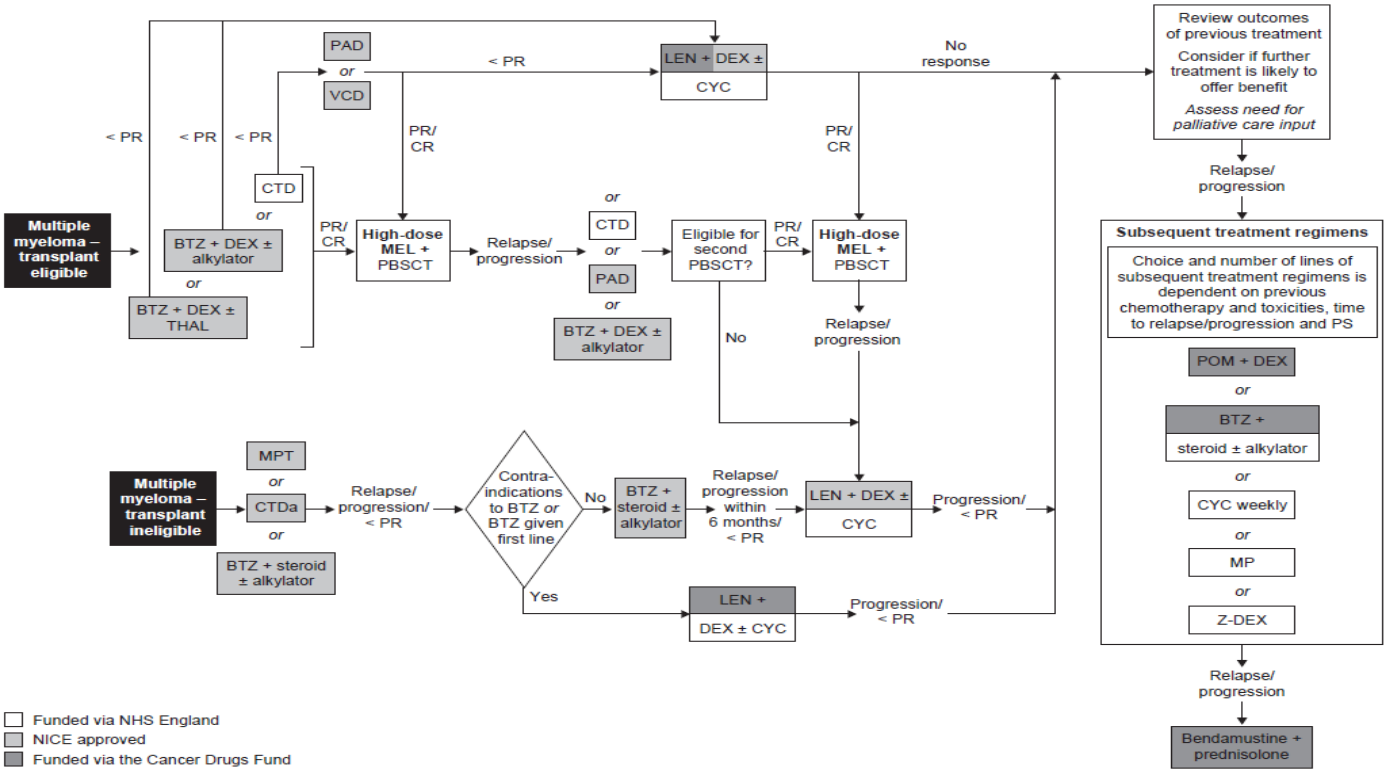
The BCSH guidelines note that many UK patients receive thalidomide (THAL)-based therapy at induction (with or without ASCT) and it is recommended that at first relapse, these patients should be considered for bortezomib-based therapy. It is noted however that bortezomib-based therapy may not be the best choice for patients who received thalidomide-based induction therapy if they have pre-existing peripheral neuropathy or immobility or lack venous access. The guidelines also note that if patients enjoyed a long plateau response to thalidomide, and bortezomib is unsuitable for them, they may well respond again to thalidomide at relapse.

For patients at second or subsequent relapse, or patients at first relapse who are intolerant of thalidomide or bortezomib, the BCSH guidelines recommend that treatment with lenalidomide (LEN) be considered. At the second or subsequent relapse, it is recommended that bortezomib -based therapy should be offered for patients with renal failure.

The BCSH guidelines highlight that, unless contraindicated, treatment with thalidomide, bortezomib or lenalidomide should be delivered with dexamethasone (with or without chemotherapy) in order to increase response rates. In the management of relapsed MM, the BCSH guidelines note that single agent activity of novel agents is limited and therefore that these agents should normally be given in combination to maximize benefit.

The draft National Chemotherapy Algorithm for Multiple Myeloma (v.0.7) provides a thorough picture of the currently available and reimbursed treatment pathways for both transplant ineligible and eligible patients (Figure 4). First-line and second-line treatment is dependent on transplant eligibility. Subsequent treatments follow the same pattern regardless of transplant eligibility (or renal impairment) and there are limited options.

Figure 4 Algorithm for the management of multiple myeloma in patients ineligible and eligible for ASCT



ASCT, autologous stem cell transplantation; BTZ, bortezomib; CR, complete response; CTD, cyclophosphamide, thalidomide and dexamethasone; CYC, cyclophosphamide; DEX, dexamethasone; LEN, lenalidomide; MEL, melphalan; MP, melphalan and prednisone; MPT, melphalan, prednisolone and thalidomide; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PAD, bortezomib, doxorubicin and dexamethasone; PBSCT, Peripheral blood stem cell transplantation; POM, pomalidomide; PR, partial response; PS, performance status; THAL, thalidomide; VCD, bortezomib, cyclophosphamide and dexamethasone; Z-DEX, oral idarubicin and dexamethasone.

National Chemotherapy Algorithms[79]

Achievement of at least a complete response (CR) or near-complete response (nCR) is associated with a prolonged TFI and hence improved HRQL

The BCSH guidelines note that many studies in both the transplant and non-transplant settings suggest a link between the maximal response attained after initial therapy and long-term outcomes, with increased remission rates resulting in prolonged PFS. Furthermore, analysis of data for the pivotal bortezomib trial, APEX, has shown that achievement of a complete response (CR) with BTZ/DEX is associated with a significant increase in the duration of the TFI from 6 to 7 months for patients achieving a partial response (PR) or very good partial response (VGPR) to 24 months for patients achieving a CR.[19] Given that a longer TFI is associated with improved HRQL (see section 3.2), achieving a CR or near-complete response (nCR) is clearly a valuable therapeutic goal for patients with rrMM.

Panobinostat in combination with BTZ/DEX extends and widens treatment options for patients with rrMM

Within the existing treatment pathways followed for the care and management of patients with rrMM, it is envisaged that panobinostat plus BTZ/DEX would be used as an alternative to BTZ/DEX at first or subsequent relapse. This extends and widens treatment options for patients with rrMM. As demonstrated in the PANORAMA-1 study (see section 4.7), the addition of panobinostat to BTZ/DEX prolongs PFS and the duration of the TFI. This thus provides patients with an extended period in remission together with an extended period without treatment and hence a better HRQL than that achieved with BTZ/DEX.

3.4 Life expectancy and potential patient population

Median overall survival from second-line treatment is less than 2 years

MM has a high fatality rate and median OS is approximately 5 years from diagnosis,[80,81] although survival can vary from a matter of months to more than 10 years.[52] Factors affecting survival include burden of disease, type of cytogenetic abnormality, age, performance status and response to treatment. [82]

Large-scale epidemiological studies show that the survival of patients diagnosed with MM between 2003 and 2009 is better than for those who were diagnosed in the late 1980s.[83] The later period corresponds with the time during which novel agents were introduced for the treatment of MM. However, despite temporal trends showing reductions in MM mortality, long-term survival is still poor in the UK, where age-standardised survival rates are 77% at one year, falling to 47% at 5 years and 33% at 10 years (estimated for 2010 to 2011).[84] Data from the HMRN in relation to a cohort of 1645 MM patients diagnosed between September 2004 and August 2011, reported that median OS was

2.5 years for the group overall.[60] Furthermore, for patients receiving second-line therapy, the median OS was 1.2 years from the start of second-line treatment.

Approximately 1300 patients in England and Wales would be eligible to receive panobinostat annually

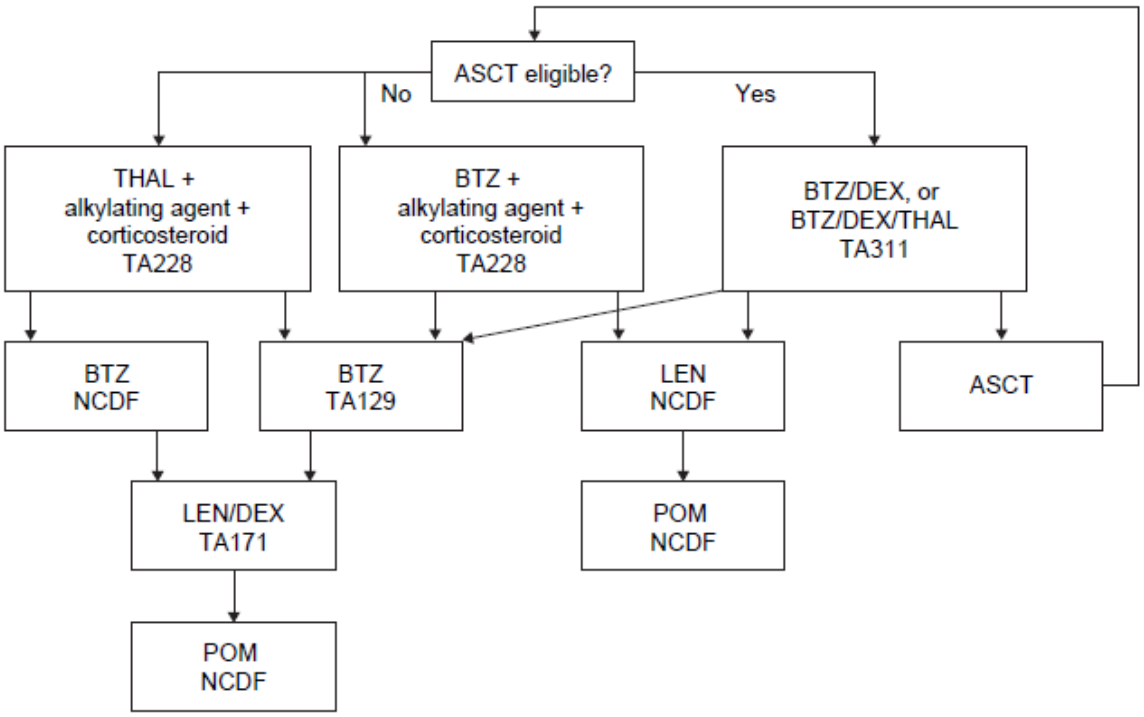
The therapeutic indication for panobinostat relates to the treatment of patients with rrMM. There is a lack of epidemiological data specific to patients with rrMM, but figures are available for the number of people with MM in the UK. In 2011, NICE stated in Technology Appraisal (TA) 228 that in England and Wales there were approximately 3600 new diagnoses of MM recorded annually.[52] The same document suggested that at that time there were between 10,000 and 15,000 people living with MM in the UK.[52] According to the current Cancer Research UK data, there were 4792 UK diagnoses of MM (4039 in England) in 2011 and 2742 deaths due to MM in 2012.[82] The figures from Cancer Research UK also report that 37% of patients with MM in England survived their cancer for 5 years or more in the period 2005 to 2009.[84] Recent Cancer Research UK and HMRN data suggest there are 3117 patients with MM in England and Wales, of whom 2194 will be receiving active treatment in first line setting of which 86.5% receives 2nd line treatment where the bortezomib treatment rate is approximately 71%.

Data from the HMRN for a cohort of 1645 MM patients diagnosed between September 2004 and August 2011 reported that for 2011, 56.3% of patients received thalidomide (THAL)-based therapy, 15.6% received lenalidomide (LEN)-based therapy and 9.4% received bortezomib (BTZ)-based therapy as first-line treatment. These data suggest that approximately 90% of patients receiving second-line therapy would be naïve for bortezomib and hence could be considered for panobinostat triplet therapy (PANO/BTZ/DEX).[60] Treatment pathways for MM have evolved significantly in the UK since 2011 with changes in the regimens approved for reimbursement via the National Cancer Drug Fund (NCDF) and NICE (TA311).[85] Thus the findings of the HMRN audit may not precisely represent current practice but are nevertheless relevant to this submission.

3.5 NICE guidance

There is currently no overarching clinical guidance provided by NICE specifically on the management of MM, although a guideline is in development as part of the clinical guidelines wave, due January 2016.[86] There are however a number of NICE TAs that provide guidance on recommended lines of treatment appropriate for use in the management of patients with MM or rrMM, and the current NCDF List (Version 3.0 12 January 2015) also serves to define and describe how non-NICE-approved therapies (licensed and unlicensed) for MM may be funded (Figure 5).[52,85,87-89]

Figure 5 Treatment algorithm for the management of multiple myeloma in England and Wales based on NICE recommendations and NCDF reimbursement approval



Note – NCDF funded options are only available in England.

ASCT, autologous stem cell transplantation; BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; NCDF, National Cancer Drugs Fund; NICE, National Institute for Health and Care Excellence; POM, pomalidomide; TA, technology appraisal; THAL, thalidomide.

A series of NICE TAs focus on licensed therapies of the IMiD and PI classes.

The first of these, published in October 2007 (NICE TA129),[88] recommends the proteasome inhibitor bortezomib as a monotherapy option for the treatment of progressive MM in people who are at first relapse, having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation. Specifically, bortezomib monotherapy is recommended for use under the following conditions, namely that: the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in people who have a CR or a PR (ie, a reduction in serum M protein of 50% or more or, where serum M protein is not measurable, an appropriate alternative biochemical measure of response is achieved); and that the manufacturer rebates the full cost of bortezomib for people who, after a maximum of four cycles of treatment, have less than a PR (as defined above). However, bortezomib as monotherapy is not a preferred option in UK clinical practice. Bortezomib is usually given in combination, most frequently with dexamethasone. The recent HMRN audit suggests that within the audit cohort bortezomib was given as monotherapy in only 10.3% (20/193) of all the cases of bortezomib use second-line. These 20 cases represent 4.5% of all second-line treatments within the cohort.

The NICE TA171 (first published in June 2009 and updated in April 2014) recommends the IMiD lenalidomide, in combination with dexamethasone, as an option in people with MM who have had at least two prior therapies, conditional on the drug cost of lenalidomide (excluding any related costs) for people who remain on treatment for more than 26 cycles (each cycle of 28 days; normally a period of 2 years) being met by the manufacturer.[87]

In July 2011, NICE published TA228 which considers the role of bortezomib and thalidomide for the first-line treatment of MM.[52] This guidance recommends thalidomide in combination with an alkylating agent and a corticosteroid as an option for first-line treatment in patients for whom high-dose chemotherapy with ASCT is considered inappropriate. The guidance also recommends bortezomib in combination with an alkylating agent and a corticosteroid as a first-line treatment option in patients who are ineligible for ASCT if those patients are also unable to tolerate or have contraindications to thalidomide.

The most recent positive NICE guidance pertaining to MM is NICE TA311, published in April 2014.[90] This guidance focuses on induction regimens for patients with untreated MM who are eligible for ASCT. The guidance states that bortezomib is recommended as an option within its marketing authorisation, that is, in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated MM who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

The use of the IMiD pomalidomide (POM) after third or subsequent relapse (its licensed indication, in combination with dexamethasone) has not been recommended by NICE.[91]

The most recent NCDF List of January 2015 provides the following guidance in relation to a number of therapies that may be considered in clinical practice as treatment options that may be funded for patients with MM:

- Bortezomib is listed as an option for the treatment of bortezomib-naïve patients at second or subsequent relapse (ie in patients who have not received bortezomib as a first or second-line therapy per NICE guidance). As of April 2015, there has been a change to the list such that bortezomib is no longer funded as a treatment for relapsed MM in patients who had received a prior course of bortezomib and had experienced a previous PR or CR of six months duration or longer.
- Lenalidomide in combination with dexamethasone may be used as a second-line treatment for MM where bortezomib is contraindicated or where bortezomib was used in the first-line setting.
- The NCDF may fund pomalidomide in combination with dexamethasone for the treatment of rrMM in patients with a performance status of 0 to 2, who have previously had adequate trials of bortezomib, lenalidomide and alkylating agents, have failed or are intolerant to bortezomib

and lenalidomide, are refractory to previous treatments and have no resistance to high-dose dexamethasone and no peripheral neuropathy higher than grade 2.

- Bendamustine is listed as an option, albeit unlicensed in the indication, for the treatment of relapsed MM where other treatments are contraindicated or inappropriate.[89]

3.6 Clinical guidelines

See section 3.3 for details of existing clinical guidelines relating to the management of rrMM.

3.7 Issues relating to current clinical practice

There are a number of issues relating to current management of rrMM in the UK.

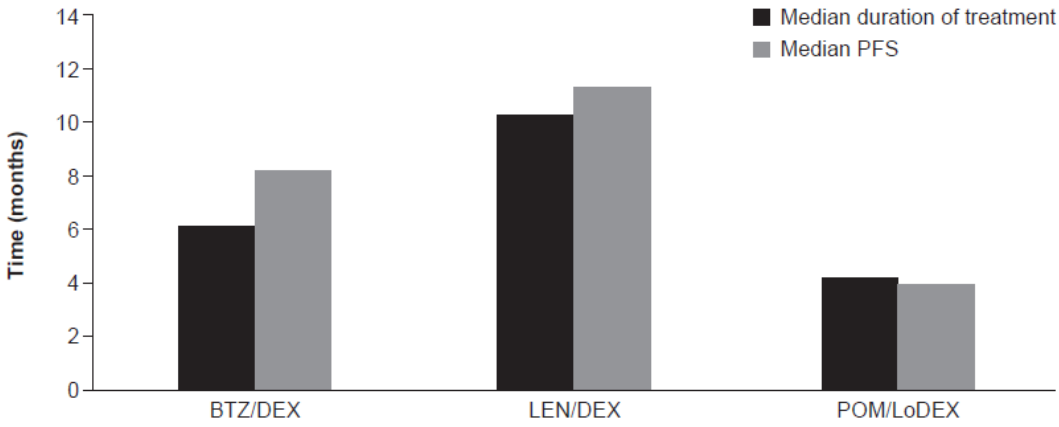
There is no single recommended regimen for the management of patients with rrMM

The available NICE guidances and the NCDF listing in effect set a clear structure for the rrMM treatment pathway. However, within the framework provided by NICE guidance and the NCDF defined access, treatment decisions in the clinic are made on an individual patient basis, based on clinical judgement and taking into account a host of factors such as the timing and frequency of relapse, the treatment history with a focus on the efficacy and toxicity profile of the different drugs used in prior lines of therapy, the patient's age and comorbidities and their bone marrow and renal function.[51]

Patients receiving currently available treatments for rrMM rarely achieve prolonged TFIs

Despite therapeutic advances, patients receiving currently available treatments for rrMM rarely achieve a prolonged TFI, unless receiving a successful stem cell transplantation, and are therefore unable to benefit from the improvements in HRQL that are associated with being off therapy.[23,57] Indeed the duration of the TFI in patients with rrMM following treatment with BTZ/DEX, an option considered for many patients at relapse following first-line therapy, is limited (eg a mean of 3.9 months as reported for PANORAMA-1, see section 4.7.5).[92] Figure 6 summarises the median TTP/PFS and treatment duration for current standard regimens based on results reported in pivotal trails and further illustrates the limited duration of the TFI. When patients receive LEN/DEX at second or subsequent relapse, treatment is given continuously until disease progression; thus patients do not benefit from a period of treatment-free remission. Regimens that can provide a longer TFI would be expected to benefit patients.

Figure 6 Median progression-free survival or time to progression and treatment duration for current standard treatments as reported in pivotal trials



BTZ/DEX: PFS, 8.1 months; DoT, 6.1 months[9]

LEN/DEX: PFS, 11.1 months; DoT; 10.1 months[93]

POM/DEX: PFS, 4.0 months; DoT, 4.2 months[94]

BTZ, bortezomib; DEX, dexamethasone; DoT, duration of treatment; LEN, lenalidomide; LoDEX, low dose dexamethasone; POM, pomalidomide; PFS, progression free survival

San Miguel et al 2014;[9] Dimopolous et al 2009;[93] San Miguel et al 2013[94]

Few patients with rrMM achieve a CR or nCR with available drug regimens

Another challenge is that currently few patients with rrMM achieve a CR or nCR with available drug regimens as illustrated in Table 5. For example, data from pivotal clinical studies with bortezomib and LEN/DEX in rrMM report a CR rate of 6% and nCR rate of 7% for bortezomib, and corresponding response rates of 16% (CR) and 8.5% (nCR) for LEN/DEX.[20,95] This observation is pertinent because achievement of better quality responses is associated with improvements in PFS and OS,[96],[16,17] as well as a prolonged TFI.[19] Furthermore, the achievement of deep and durable responses is important in MM because it is well known that with each subsequent line of therapy the duration of response diminishes.[47] In addition, each line of therapy employed narrows the prospects for future therapeutic manoeuvres. There is thus a need for regimens which enable patients to achieve at least a VGPR.

Table 5 Summary of CR/nCR rates reported for regimens for rrMM

Study/Reference	Treatment	CR/nCR
MM-009/010[93]	LEN/DEX	24.35%
PANORAMA-1[9]	BTZ/DEX	15.75%
DOXIL-MMY-3001[21]	BTZ/DOX	12.96
APEX[94]	BTZ	12.39%
APEX[94]	DEX	1.51%

BTZ, bortezomib; CR, complete response; DEX, dexamethasone; DOX, doxorubicin; LEN, lenalidomide; nCR, near-complete response; POM, pomalidomide; rrMM, relapsed/refractory multiple myeloma.
Dimopolous et al 2009;[93] San Miguel et al 2014;[9] Richardson et al 2005;[20] Orlowski et al 2007[21]

3.8 Equality

No equality issues have been identified with the use of panobinostat for the treatment of MM.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

4.1.1 Search strategy

A clinical systematic review (up to June 2013) and updates (to May 2014 and December 2014) were performed. Clinical studies of interest included those specifically focused in rrMM of phase 2 – 4 trials reporting primary outcome data in English for the following agents: thalidomide, lenalidomide, bortezomib, pomalidomide, carfilzomib, panobinostat, daratumumab, elotuzumab and ixazomib. References reporting phase 1/2 studies (unless phase 2 results were separately reported), analyses of prognostic factors, studies of patients without rrMM, studies of interventions used as induction or maintenance therapy, and studies using sequential treatments rather than a single agent or treatment combination were excluded. In addition, the agents of interest listed above were to be the focus of the study, and studies with an agent of interest used in conjunction with a new treatment were not included.

Efficacy outcomes of interest were response rates (complete response [CR]; partial response [PR] and overall/objective response rate, [ORR]), time-to-progression (TTP) or progression-free survival (PFS), and overall survival (OS).

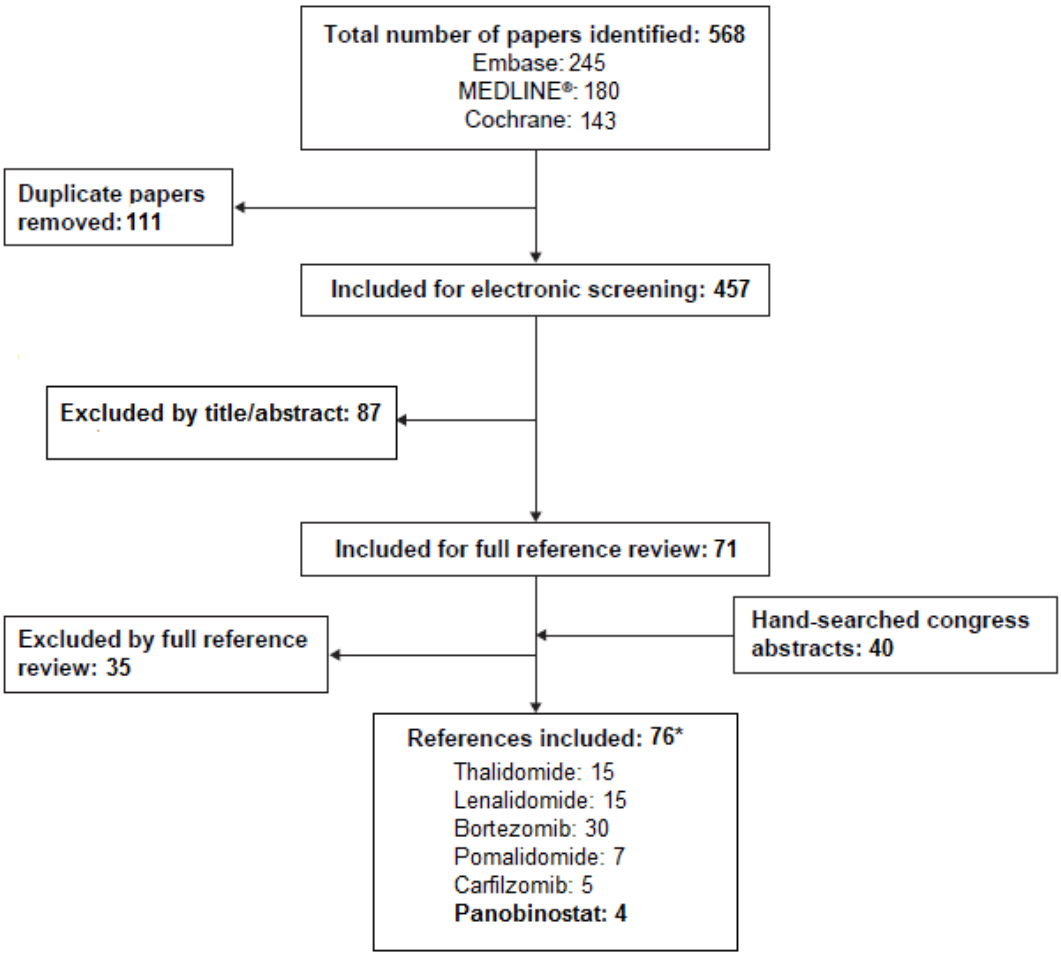
See Appendix 2 for details.

4.1.2 Study selection

To be included in this SR, references had to meet the inclusion criteria (and none of the exclusion criteria) detailed in Appendix 2. Figure 7 summarises the results of the screening.

Figure 7 PRISMA diagram of included and excluded studies in the clinical systematic review (June 2013) and May 2014 and December 2014 updates of treatment for relapsed/refractory MM

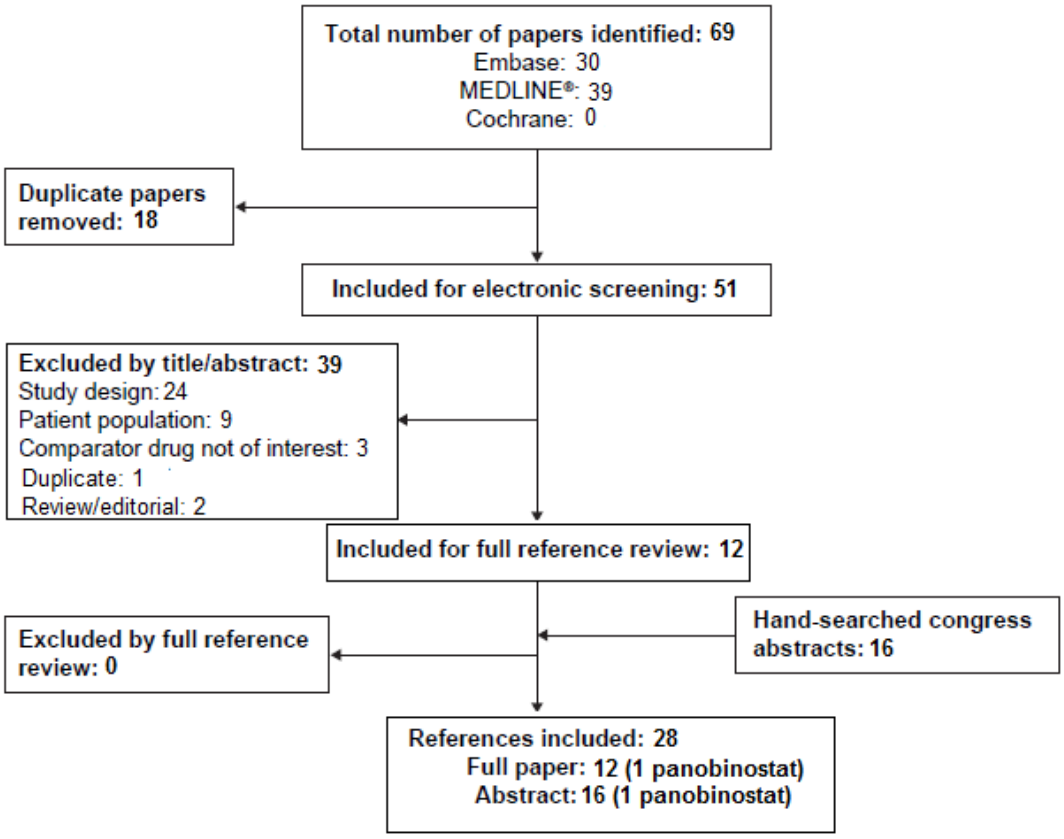
Searches conducted on 26 June 2013



* 1 study contained data on 2 relevant compounds, thus the breakdown by drug sums up to 77.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

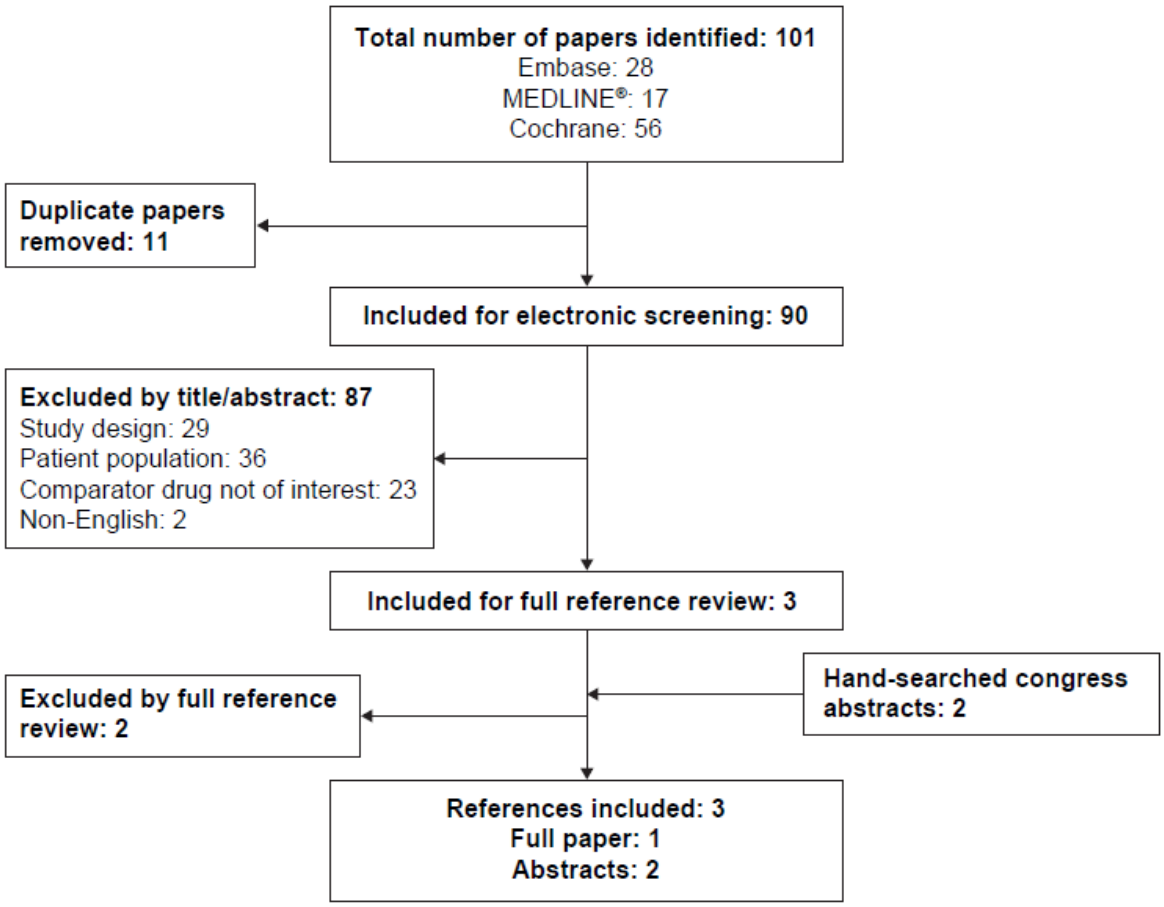
Searches conducted 16[a] and 19[b] May 2014



[a]Electronic searches; [b]Manually searched congress abstracts.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Searches conducted 2 December 2014



Of these three results derived from the final search (2 December 2014), only the panobinostat (PANORAMA-1) publication and an abstract reporting a further analysis from this study were deemed appropriate for inclusion.[9,97,98] A correction to the primary paper was published in January 2015.[98]

Data for the pivotal phase 3 PANORAMA-1 study are taken from the primary publication (including the Supplementary Appendix and the correction published in January 2015), data presented at the 2014 American Society of Clinical Oncology (ASCO) Annual Meeting and the American Society of Hematology (ASH) Annual meeting, and the Clinical Study Report (CSR).[9,98-100] Further data included in the FDA Briefing Document for the Oncology Drugs Advisory Committee (ODAC) meeting of 6 November 2014 are also included.[25] Data for the phase 2 PANORAMA-2 trial are taken from the primary publication.[101]

4.2 List of relevant randomised controlled trials

One relevant randomised controlled trial (RCT), PANORAMA-1, was identified (see Table 6). The PANORAMA-1 trial compares PANO/BTZ/DEX with BTZ/DEX and is directly relevant to the decision problem. There are no trials that directly compare PANO/BTZ/DEX with LEN/DEX or with any other treatments for MM.

Table 6 List of relevant randomised controlled trials of panobinostat in relapsed/refractory multiple myeloma.

Trial number (acronym)	Intervention	Comparator	Population	Primary study reference
PANORAMA-1 NCT01023308	PANO/BTZ/DEX	Placebo (PBO)/BTZ/DEX	Patients with rrMM who have received 13 previous treatment regimens	San-Miguel *et al*. *Lancet Oncol* 2014;15:1195–206[9] including Supplementary Appendix and a correction to the original paper published as *Lancet Oncol* 2015;16:e6[98]

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; PBO, placebo; rrMM, relapsed/refractory multiple myeloma.

4.3 Summary of methodology of the relevant randomised controlled trial

4.3.1 Design

Table 7 summarises the methodology for the PANORAMA-1 trial, a phase 3, multicentre, randomised, double-blind, placebo-controlled study of PANO/BTZ/DEX in patients with rrMM who have received between one and three prior treatment regimens.[9] Patients were randomly assigned (1:1) via an interactive web-based and voice-response system, stratified by number of previous treatment lines and by previous use of bortezomib, to receive placebo or panobinostat, both in combination with bortezomib and dexamethasone. Patients, physicians and the investigators who carried out the data analysis were masked to treatment allocation. No crossover between treatment groups was allowed.

4.3.2 Patients

Patient eligibility criteria for the PANORAMA-1 study are summarised in Table 7. The study involved patients with relapsed or relapsed and refractory MM who had received one to three previous treatments. The inclusion and exclusion criteria largely correspond to those employed in the phase 2 PANORAMA-2 study, except that patients who were refractory to bortezomib were excluded.

Table 7 Summary of the methodology for the PANORAMA-1 study.

Study details	PANORAMA-1
Location	215 centres in 34 countries
Design	Phase 3, multicentre, multinational, randomised, double-blind, placebo-controlled, parallel-group study, divided into two phases: a) treatment phase 1: 24 weeks (8 cycles of 21 days' duration each) b) treatment phase 2: 24 weeks (4 cycles of 42 days' duration each)
Eligibility criteria	**Inclusion criteria** Aged 18 years and older Measurable relapsed or relapsed and refractory MM 1 to 3 previous treatments Eastern Cooperative Oncology Group performance status of ≤ 2 ANC ≥ 1.5×10^9 cells/L Platelet count ≥ 100×10^9 cells/L Serum creatinine ≤ 1.5 × ULN Creatinine clearance ≥ 60 mL/min Normal electrolytes ≤ 1.5 × ULN Normal liver function ≤ 1.5 × ULN **Exclusion criteria** Primary refractory or BTZ-refractory MM Received previous treatment with a deacetylase inhibitor Received previous anti-myeloma treatment within 3 weeks before the start of the study Received experimental treatment or biological immunotherapy (including monoclonal antibodies) within 4 weeks before the start of the study Received previous radiation therapy within 4 weeks before the start of the study Needing valproic acid for any medical condition during the study or within 5 days prior to panobinostat /study treatment PN ≥ grade 2 Impaired cardiac function (QTcF > 450ms) or gastrointestinal function Any other clinically significant heart disease or vascular disease Allogeneic stem cell transplant recipient with GVHD (active or on immunosuppression) Intolerance to BTZ or DEX Secondary primary malignancy within < 3 years of first dose of study treatment Major surgery ≤ 2 weeks prior to starting study drug Evidence of mucosal or internal bleeding Unresolved diarrhoea ≥ CTCAE grade 2 History of HIV seropositivity Pregnancy or breast feeding

Study details	PANORAMA-1
Settings and locations where the data were collected	215 centres in 34 countries including the following sites in the UK: University College Hospital, London (n = 11) St Bartholomew's Hospital, London (n = 9) Kings College Hospital, London (n = 5) New Cross Hospital, Wolverhampton (n = 2) Christie Hospital, Manchester (n = 2) Aberdeen Royal Infirmary, Scotland (n = 1)
Intervention(s) and comparator(s)	PANO/PBO (20 mg oral) three times a week, BTZ (1.3 mg/m^2 IV) twice a week, DEX (20 mg oral) four times a week, all administered at week 1 and week 2 followed by 1 week off treatment during phase 1. Treatment during phase 2 was identical with that during phase 1 except that BTZ was administered once a week Intervention, n = 387 Comparator, n = 381 Concomitant medications: prophylactic anti-emetics, growth factor support for anaemia and neutropenia if initiated before study entry; bisphosphonates if started before the start of screening; low molecular weight heparin or vitamin K inhibitors;
Primary outcomes (including scoring methods and timings of assessments)	PFS; response was assessed at 3-week intervals during treatment phases and at 6-week intervals thereafter according to modified EBMT criteria
Secondary outcomes (including scoring methods and timings of assessments)	OS ORR (CR, nCR and PR), MRR, TTR, TTP and DOR Safety (adverse events, ECG, laboratory parameters) HRQL (EORTC QLQ-C30 and QLQ-MY20, FACT/GOG-Ntx) PK of PANO and BTZ in a subset of Japanese patients Exploratory objectives: VGPR (IMWG 2008 criteria) and sCR
Pre-planned subgroups	Included: race, gender, age (< 65 versus ≥ 65 years; ISS stage (I versus II/III); renal impairment; number of prior lines of therapy (1 versus 2 or 3); prior use of BTZ; prior ASCT; prior use of IMiDs; prior use of BTZ; geographical region; MM characteristics (relapsed versus refractory/relapsed); cytogenetic risk (normal or poor)

ANC, absolute neutrophil count; ASCT, autologous stem cell transplantation; BTZ, bortezomib; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DEX, dexamethasone; DOR, duration of response; EBMT, European Group for Blood and Bone Marrow Transplant; ECG, electrocardiogram; EORTC, European Organisation for Research and Treatment of Cancer; FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group – Neurotoxicity; GVHD, graft-versus-host disease; HIV, human immunodeficiency virus; HRQL, health-related quality of life; IMiDs; immunomodulatory drugs; IMWG, International Myeloma Working Group; IV, intravenous; MM, multiple myeloma; MRR, minimal response rate; nCR, near-complete response; ORR, overall response rate; OS, overall survival; PANO, panobinostat; PBO, placebo; PFS, progression-free survival; PK, pharmacokinetics; PN, peripheral neuropathy; PR, partial response; QLQ-C30, Quality of Life Questionnaire – Core 30; QLQ-MY20, Quality of Life Questionnaire – Multiple Myeloma 20; QTcF, QT interval corrected for heart rate by use of Fridericia's QT formula; sCR, stringent complete response; TTP, time to progression; TTR, time to response; ULN, upper limit of normal; VGPR, very good partial response.

4.3.3 Treatment

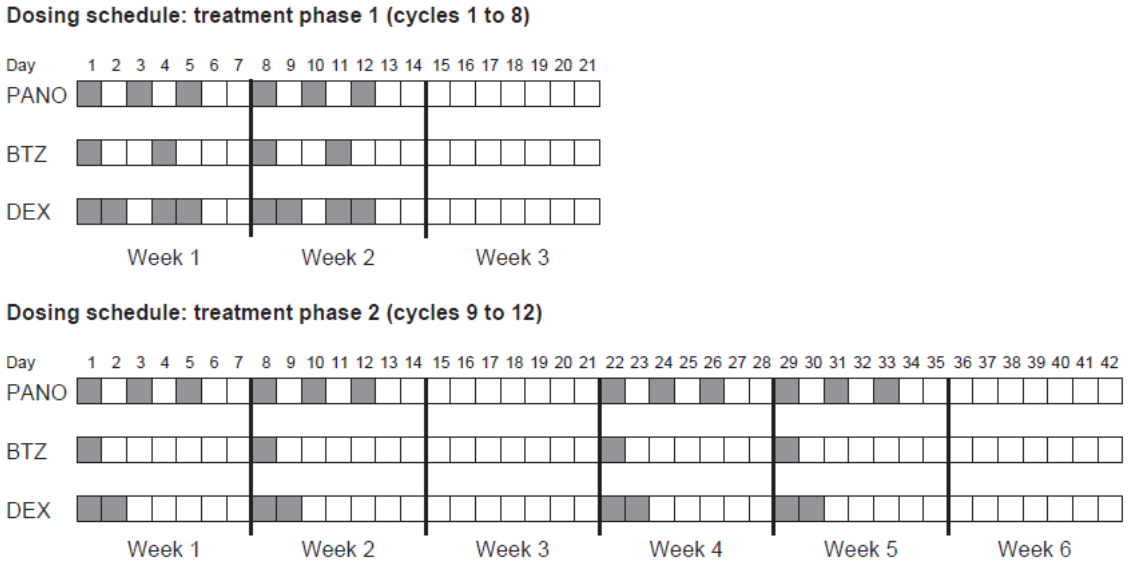
Dose selection rationale

The dose and schedule of panobinostat used in PANORAMA-1 was selected based on the following rationale and clinical experience in the phase 1/2 program. Single-agent oral panobinostat was first tested in patients with MM in the dose-escalation phase 1 study, B2102, and in the phase 2 PANORAMA-2 study in MM (see section 4.11). These trials showed tumour responses in patients with cutaneous T-cell lymphoma, Hodgkin's lymphoma, acute myeloid leukaemia, myelofibrosis and MM at doses of ≥ 20 mg used in various schedules. In addition, these single-agent studies suggested that sustained histone acetylation was achieved in peripheral blood mononuclear cells up to one week after dosing at doses ≥ 20 mg. Based on 15 evaluable patients included in the phase 1 study, the maximum tolerated dose was declared at 20 mg panobinostat three times a week and 1.3 mg/m^2 bortezomib. Subsequently, on the basis of a pooled analysis and a pharmacokinetic-pharmacodynamic modelling of single-agent panobinostat-induced thrombocytopenia suggesting that drug holidays should be effective to allow recovery of platelet counts, a dosing schedule of 2 weeks on and 1 week off at 20 mg panobinostat was introduced into the dose expansion phase of the phase 1 study and in PANORAMA-1 to manage thrombocytopenia and to allow for accelerated platelet recovery.

Regimens

The study included two treatment phases with a maximum total duration of 12 cycles (Figure 8). In treatment phase 1 (consisting of eight 3-week cycles), patients received oral panobinostat (20 mg) or placebo three times a week for the first two weeks, and intravenous bortezomib (1.3 mg/m^2) on days 1, 4, 8 and 11. Oral dexamethasone (20 mg) was given on each day of bortezomib administration and the following day (days 1, 2, 4, 5, 8, 9, 11 and 12). At the end of treatment phase 1, patients with clinical benefit, defined as at least no change on day 1 of cycle 8 (as assessed by the modified European Group for Blood and Marrow Transplantation [EBMT] criteria),[46] could proceed to treatment phase 2 (consisting of four 6-week cycles), in which panobinostat or placebo was given on a similar schedule, bortezomib was given once a week during weeks 1, 2, 4 and 5, and dexamethasone was given on each day of bortezomib administration and on the following day.

Figure 8 Dosing schedules in treatment phases 1 and 2 of the PANORAMA-1 study.



BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

Dose delays and reductions were permitted for study treatment toxic effects, including: grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding: grade 4 neutropenia (absolute neutrophil count of 0.5 $\times 10^9$ cells/L) or persistent neutropenia (at least two occurrences within a cycle) with absolute neutrophil count between 0.5 $\times$ 10^9 and 0.75 $\times$ 10^9 cells/L; grade 3 or 4 anaemia; grade 2 diarrhoea; grade 4 vomiting or grade 3 vomiting uncontrolled by standard anti-emetic drugs; grade 3 to 4 fatigue; grade 3 to 4 hyperbilirubinaemia; or more than five times the upper limit of normal aspartate aminotransferase or alanine aminotransferase levels.

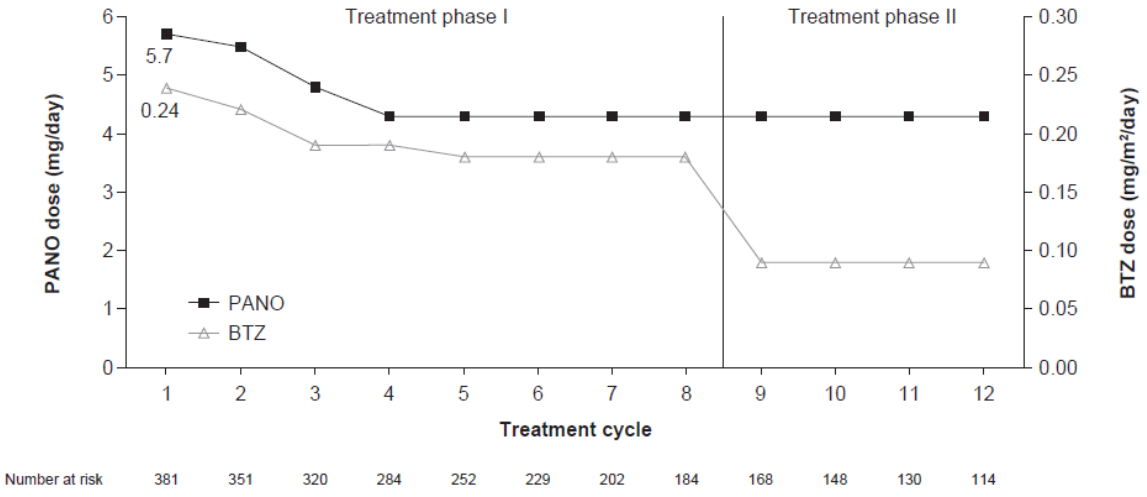
The dose of panobinostat/placebo could be modified during any cycle as follows: for patients receiving 20 mg three times a week the dose could be reduced to 15 mg/day and for those receiving 15 mg/day, the dose could be reduced to 10 mg/day. Dose levels of less than 10 mg three times a week in combination with a minimum bortezomib dose of 0.7 mg/m^2, with or without dexamethasone, were not permitted at any time during the study. If it was determined that a patient required a panobinostat dose below 10 mg three times week in combination with the minimum dose of bortezomib, the patient was discontinued from study treatment. Patients who could not tolerate panobinostat, placebo or bortezomib were required to permanently discontinue treatment, but were followed for disease assessment and survival. Patients who could not tolerate dexamethasone were permitted to continue treatment without dexamethasone. Figure 9 shows the median intensity of the panobinostat and bortezomib per treatment cycle administered during the study.

The dose and schedule of administration of panobinostat in the PANORAMA-1 study was the same as that used in the phase 2 PANORAMA-2 study (see section 4.11) and was chosen on the basis of the results of single-agent phase 1 studies in a range of haematological malignancies which demonstrated responses with doses of 20 mg/day or greater.[25] Furthermore, a phase 1b study in

patients with rrMM established a dose of 20 mg as the maximum tolerated dose in combination with bortezomib and dexamethasone (see section 4.11). A pooled analysis and modelling of thrombocytopenia associated with panobinostat therapy suggested that a dosing schedule consisting of two weeks on therapy and one week off panobinostat would allow recovery of platelets between cycles and was investigated the phase 2, PANORAMA-2. This was then adopted for the phase 3 PANORAMA-1 study.

At the time of designing the PANORAMA-1 trial, bortezomib was approved for delivery via the intravenous route and hence this was specified for the trial. More recently bortezomib has been approved for delivery via the subcutaneous route based on the results of a phase 3 trial demonstrating equivalent efficacy for both routes and a more favourable safety profile for subcutaneous delivery.[26] We believe subcutaneous delivery will be generally used in routine clinical practice.

Figure 9 Median dose intensity of panobinostat and bortezomib in the PANO/BTZ/DEX group by treatment cycle in the PANORAMA-1 study



BTZ, bortezomib; PANO, panobinostat.
San Miguel et al 2014[97]

4.3.4 Efficacy outcomes

The primary endpoint was PFS (as assessed by the investigators on the basis of the modified EBMT criteria), which was defined as the time from randomisation until documented disease progression, relapse from CR, or death, whichever came first (Table 8). The key secondary endpoint was OS, which was defined as the time from randomisation to death from any cause. Other secondary endpoints included the proportions of patients with an overall response (ORR, ie ≥ PR), nCR, CR or minimal response (MR), response duration (from first occurrence of ≥ PR), time to progression (TTP,

time from randomisation to first documented disease progression or relapse) and safety. The following assessments of HRQL and symptoms were also included: European Organization for Research and Treatment of Cancer [EORTC] quality of life questionnaire-core 30 [QLQ-C30]; Functional Assessment of Cancer Therapy [FACT]/Gynaecologic Oncology Group [GOG] Neurotoxicity [Ntx] [FACT/GOG-Ntx]; and the EORTC MM-specific module [QLQ-MY20])

Table 8 Primary and secondary outcomes for the PANORAMA-1 study.

Trial	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/ current use in clinical practice
PANORAMA-1	The primary endpoint was PFS (as assessed by the investigators on the basis of the modified EBMT criteria), and was defined as the time from randomisation until documented disease progression, relapse from complete response, or death, whichever came first	PFS is a recognised outcome measure for assessment of treatments for MM.[102-104] Unlike OS, it is not influenced by therapy following relapse and therefore can be a more accurate measure of treatment efficacy	Key secondary endpoint: OS Other secondary outcomes: ORR (CR, nCR and PR), MRR, TTR, DOR and TTP Safety (adverse events, ECG, laboratory parameters) HRQL (EORTC QLQ-C30 and QLQ-MY20, FACT/GOG-Ntx) Exploratory endpoints: VGPR (IMWG 2008 criteria) and sCR PK of PANO and BTZ in a subset of Japanese patients	OS is a well-recognised outcome measure for treatments of MM because therapies aim to prolong survival. ORR (CR, nCR and PR) are recognised measures of efficacy in MM as defined using the EBMT criteria[103,104]

BTZ, bortezomib; CR, complete response; DOR, duration of response; EBMT, European Group for Blood and Bone Marrow Transplantation Organization; ECG, electrocardiogram; EORTC, European Organisation for Research and Treatment of Cancer; FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group – Neurotoxicity; HRQL, health-related quality of life; IMWG, International Myeloma Working Group; MM, multiple myeloma; MRR, minimal response rate; nCR, near-complete response; ORR, overall response rate; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; QLQ-C30, Quality of Life Questionnaire – Core 30; QLQ-MY20, Quality of Life Questionnaire – Multiple Myeloma 20; sCR, stringent complete response; TTP, time to progression; TTR, time to response; VGPR, very good partial response

4.3.5 Pre-planned subgroup analyses

Pre-planned subgroup analyses were performed for the primary endpoint, PFS, including: ethnic origin; gender; age group; International Staging System stage; renal impairment; number of previous lines of therapy and previous use of bortezomib; ASCT; IMiDs; IMiDs and bortezomib; geographical region; relapsed and refractory versus relapsed disease; and cytogenetic risk group. Cytogenetic

analysis was carried out by fluorescent *in situ* hybridisation. The cytogenetic poor-risk group includes patients with any of the following three cytogenetic abnormalities at baseline: t(4;14); t(14;16); and 17p deletion. The cytogenetic normal-risk group includes patients with none of the poor-risk cytogenetic abnormalities at baseline. Results for the pre-planned subgroups are reported in section 4.7.2 and the results of further subgroup analyses are presented in section 4.8.

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trial

Table 9 summarises the statistical analyses employed for the PANORAMA-1 trial.

4.4.1 Populations

Efficacy assessments including analysis of the primary and secondary endpoints were performed using the full analysis set (ie, all randomly assigned patients) and safety analysis were done for the safety set (patients who received one dose of any component of study treatment).

4.4.2 Sample size calculation

To determine the sample size needed, median PFS was assumed to be 10.2 months for PANO/BTZ/DEX and 7·5 months for the control group (BTZ/DEX) (hazard ratio [HR] 0·74). PFS was censored at the date of the last adequate assessment before the analysis cut-off date or start of new anti-neoplastic treatment for patients who had not progressed or who had received a new treatment. A two-sided log-rank test with a cumulative type I error of 0·05 and a power of 90% for an assumed HR of 0·74 was used based on a sequential analysis plan with two planned interim analyses. Interim analyses were scheduled to occur after 33% and 80% of the 460 PFS events required for the final analysis were recorded. The planned second interim analysis was not performed, but the α was spent at that time point per the group sequential design. Considering the original assumption of recruitment of 30 patients per month and a final primary PFS analysis after an anticipated duration of approximately 29 months after study start, 762 patients would have to be randomised. This number acknowledges the observed rate (as of 22 November 2011) of approximately 20% for patients censored and no longer followed for disease follow-up. The final analysis for PFS is to be performed when approximately 460 events have been observed in the full analysis set.

After the OS interim analysis conducted at the time of the final PFS analysis, a second OS interim analysis with minimal alpha assigned was performed when 86.5% of the 415 events required for the final OS analysis were observed. The final OS analysis will be performed after all 415 OS events have been observed.

4.4.3 Statistical tests

The primary analysis was done with a stratified log-rank test. The HR (with two-sided 95% confidence interval [CI]) for the treatment effect PANO/BTZ/DEX over control was estimated based on a proportional hazards model that included treatment group and the two randomisation strata. OS, the key secondary endpoint, was tested only if the primary endpoint was statistically significant. The final analysis of OS is planned when 415 survival events have occurred (estimated in 2015).

Other secondary endpoints of ORR, nCR/CR rate, time to response, and response duration were calculated based on modified EGBMT criteria using the full analysis set. Point estimate and exact 95% 2-sided CI of ORR and nCR/CR rate were calculated and analysed using unadjusted Cochran-Mantel-Haenszel test based on strata at randomisation. The statistical test of nCR/CR rate was performed using post hoc analysis. Median time to response, time to progression, and response duration were estimated using the Kaplan–Meier method.

Table 9 Summary of statistical analyses used in PANORAMA-1

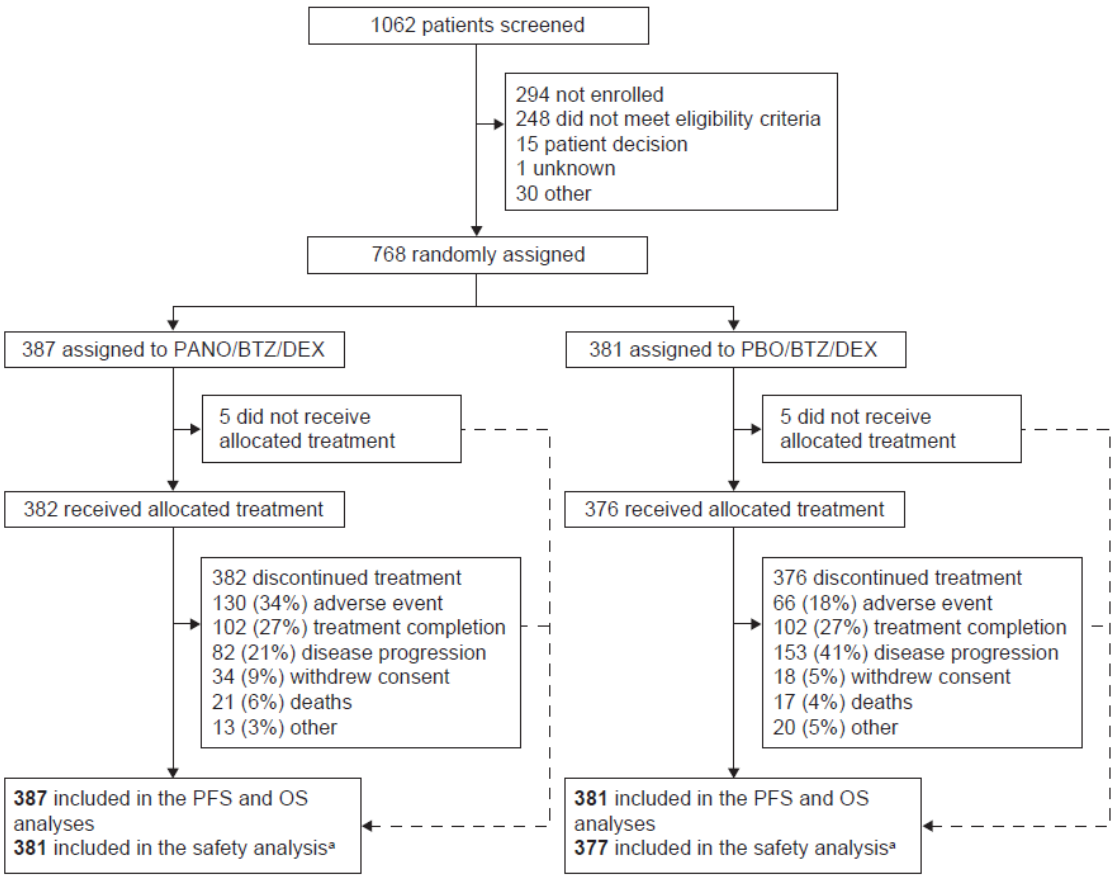
Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
PANORAMA-1	To compare PFS in patients treated with PANO in combination with BTZ/DEX versus patients treated with placebo in combination with BTZ/DEX.	The primary analysis of PFS was performed using a stratified log rank test considering a cumulative type I error rate of α = 0.05, 2-sided.	The median PFS of the PBO/BTZ/DEX and PANO/BTZ/DEX arms were assumed to be 7.5 months and 10.2 months, respectively (HR = 0.74). A two-sided log rank test with a cumulative type I error of α = 0.05 and a power of 1-β = 90% was used for the 3-look group sequential plan. Under the above assumptions and using a 1:1 randomisation to the two arms of this trial, a total of 460 PFS events were required. Considering the original assumption of recruitment of 30 patients per month and a final primary PFS analysis after an anticipated duration of approximately 29 months after study start, 762 patients would have to be randomized. This number acknowledges the observed rate (as of 22 November 2011) of approximately 20% for patients censored and no longer followed for disease follow-up. The final analysis for PFS will be performed when approximately 460 events are observed in the FAS.	Details not available

BTZ, bortezomib; DEX, dexamethasone; FAS, full analysis set; HR, hazard ratio; PANO, panobinostat; PBO, placebo; PFS, progression-free survival

4.5 Participant flow in the relevant randomised controlled trials

Patients with measurable relapsed or relapsed and refractory MM were enrolled between January 2010 and February 2012 randomly assigned to PANO/BTZ/DEX (n = 387) or placebo/BTZ/DEX (n = 381) (Figure 10).[9] As of the data cut-off in September 2013, median follow-up was approximately 2.5 years in both groups. At this time point, all patients had completed or discontinued treatment (ie treatment phases 1 and 2) and 74% of patients in each group had discontinued treatment early. A greater proportion of patients discontinued owing to disease progression in the control group (41%) than in the panobinostat group (21%). A greater proportion of patients discontinued owing to adverse events in the panobinostat group (34%) than in the control group (18%).

Figure 10 Patient disposition in the PANORAMA-1 study.



[a]One patient randomly assigned to receive panobinostat was given placebo during cycles 1 and 2 because of a misallocation error; the patient was subsequently given panobinostat from cycle 3 until discontinuation of treatment, but was included in the placebo group for safety analysis.

BTZ, bortezomib; DEX, dexamethasone; OS, overall survival; PANO, panobinostat; PBO, placebo; PFS, progression-free survival.

San Miguel et al. 2014[9]

Baseline demographic and pathological characteristics were similar in the two treatment groups (Table 10). Approximately a third of patients had relapsed and refractory disease and almost half of the patients had received two or three previous treatment regimens. Approximately 50% of patients had previously received thalidomide and 43% had previously received bortezomib.

Table 10 Characteristics of participants in the PANORAMA-1 study across randomised groups.

Characteristic	**PANORAMA-1 (n = 768)**	
	PANO/BTZ/DEX (n = 387)	**PBO/BTZ/DEX (n = 381)**
Age, years		
Mean ± SD	62.4 ± 9.34	61.8 ± 9.43
Median age (range)	63.0 (28 to 84)	63.0 (32 to 83)
Age category, n (%)		
< 65 years	225 (58.1)	220 (57.7)
> 65 years	162 (41.9)	161 (42.3)
Male, n (%)	202 (52)	205 (54)
Time since diagnosis, months		
N	386	381
Mean ± SD	46.7 ± 38.02	49.0 ± 34.78
Median (range)	37.1 (2.4 to 308.1)	38.9 (2.4 to 300.2)
ECOG performance status, n (%)		
0	175 (45)	162 (43)
1	191 (49)	186 (49)
2	19 (5)	29 (8)
Creatinine clearance, n (%)		
60 to 89 mL/min	265 (68)	249 (65)
≥ 90 mL/min	120 (31)	129 (34)
Missing	2 (< 1)	3 (< 1)
ISS staging, n (%)		
Stage I	156 (40.3)	152 (39.9)
Stage II	104 (26.9)	92 (24.1)
Stage III	77 (19.9)	86 (22.6)
Not assessed	50 (12.9)	51 (13.4)
MM characteristics, n (%)		
Relapsed and refractory	134 (35)	141 (37)
Relapsed	247 (64)	235 (62)
Other	6 (2)	5 (1)
Prior autologous stem cell transplantation, n (%)	215 (56)	224 (59)
Previous treatment lines, n (%)[a]		
N	386	381
Mean ± SD	1.7 ± 0.76	1.7 ± 0.78

Characteristic	PANORAMA-1 (n = 768)	
	PANO/BTZ/DEX (n = 387)	PBO/BTZ/DEX (n = 381)
Median (range)	1.0 (1 to 4)	1.0 (1 to 3)
1	198 (51.2)	198 (52.0)
> 2	189 (48.8)	183 (48.0)
Prior therapy, n (%)		
BTZ	169 (43.7)	161 (42)
LEN	72 (18.6)	85 (22)
THAL	205 (53.0)	188 (49)
Melphalan	310 (80.1)	301 (79.0)
DEX	308 (80)	315 (83)
BTZ/IMiD	94 (24.3)	99 (26)
BTZ/DEX	147 (38.0)	143 (38)
BTZ/LEN	34 (8.8)	45 (11.8)
DOX	129 (33)	138 (36)
VIN	115 (30)	117 (31)
Cytogenetic risk group, n (%)[b]		
N	120	124
Normal risk	79 (65.8)	88 (71.0)
Poor risk	24 (20.0)	13 (10.5)
Unknown or missing	17 (14.2)	23 (18.5)

BTZ, bortezomib; DEX, dexamethasone; DOX, doxorubicin; ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory drug; ISS, International Staging System; LEN, lenalidomide; MM, multiple myeloma; PANO, panobinostat; PBO, placebo; SD, standard deviations; THAL, thalidomide; VIN, vincristine.

[a]One patient in the PANO/BTZ/DEX group had received no previous anti-neoplastic treatments and another had received more than three previous treatments.

[b]Based on number of patients who consented for biomarker protocol

San Miguel et al. 2014;[9] FDA, 2014[25]

4.6 Quality assessment of the relevant randomised controlled trials

Table 11 provides an assessment of the quality of the PANORAMA-1 study.

The trial is in general reflective of the emerging clinical practice in England and Wales in that: 1) patients enrolled in the study were broadly representative of patients likely to receive BTZ/DEX with or without panobinostat in clinical practice; 2) the comparator (BTZ/DEX) was given mainly as a second-line treatment regimen in line with the NICE guidance TA129 and current NCDF policies (including the recent delisting of retreatment with bortezomib as an option) ; 3) thalidomide or bortezomib together with an alkylating agent and a corticosteroid are the approved first-line treatment options for transplant ineligible patients as per NICE guidance TA228; 4) lenalidomide is not yet approved for reimbursement as a first-line agent; 5) BTZ/DEX with or without thalidomide is the recommended

induction regimen for transplant eligible patients (see sections 3.3 and 3.5). Furthermore, the assessment of response to therapy used in this study is comparable to that used in routine clinical practice in the UK (although the International Myeloma Working Group [IMWG] rather than EBMT criteria are generally used in clinical practice).

However there are certain limitations in the trial design with regards to the current UK clinical practice. Firstly, use of bortezomib in the trial differs from that currently recommended by NICE (TA129),[88] in that patients received 12 cycles of therapy (unless they discontinued for toxicity), irrespective of response. This contrasts with NICE recommendations to assess response after four cycles of therapy and only continue treatment in people who have a CR or a PR, ie the so called "stopping rule" as per the NICE-approved bortezomib patient access scheme (PAS). Secondly, bortezomib was given by the intravenous route. While this matched the standard practice at the time of design of the trial, this no longer corresponds to routine clinical practice. Thirdly, the proportion of patients who had received prior stem cell transplantation in the PANORAMA-1 trial is higher than the 18% reported for current UK clinical practice.[60] (See section 4.13.4 for further details)

Table 11 Quality assessment for the PANORAMA-1 study.

PANORAMA-1		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Patients were centrally assigned to each treatment arm via IXRS in a ratio of 1:1	Yes
Was the concealment of treatment allocation adequate?	PANO and matching placebo were supplied as hard gelatine capsules. The identities of the treatments were concealed by the use of study drugs (PANO and placebo) that were identical in packaging, labelling, schedule of administration and appearance	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Treatment arms were well balanced with respect to baseline demographic characteristics	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, investigator staff, persons performing the assessments and data analysts remained blind to the identity of the treatment from the time of randomisation until final database lock	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No. Over the course of the study all patients in both groups discontinued treatment. However, the reasons for discontinuation differed between treatment groups. The most common reasons for treatment termination were adverse events (130 [34%] in the PANO group versus 66 [17%] in the placebo group) and disease progression (82 [21%] versus 153 [40%])	Yes
Is there any evidence to suggest that the	The primary outcome, key secondary	Yes

PANORAMA-1		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
authors measured more outcomes than they reported?	outcome and most other secondary outcomes listed in the CSR are reported in the primary manuscript	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes; the primary analysis was assessed in the full analysis set which included all randomised patients	Unclear

CSR, Clinical Study Report; IXRS: Interactive web-based and voice response randomization system, N/A, not applicable; PANO, panobinostat.

4.7 Clinical effectiveness results of the relevant randomised controlled trials

4.7.1 Overview

The final analysis for the primary endpoint, PFS, was performed for the data cut-off of 10 September 2013 at a median follow-up of 31 months. In this analysis the study met its primary endpoint by demonstrating a statistically significant improvement in PFS for PANO/BTZ/DEX over placebo/BTZ/DEX ($p < 0.0001$). Although ORR was the same in both groups, nCR/CR was significantly higher in the panobinostat group ($p = 0.00006$) than in the control group and other efficacy parameters showed numerical differences in favour of the panobinostat group (Table 12). The survival data are not yet mature (predicted in 2015), but a numerical survival advantage is evident for PANO/BTZ/DEX over the control group in the planned interim analysis (cut-off 10 September 2013) and in the most recent protocol-amended analysis (cut-off 18 August 2014), where approximately 90% of the target number of OS events had been reached.

Table 12 Summary of efficacy outcomes in the PANORAMA-1 study (analysis based on data cut-off, September 2013).

Best overall response per investigator assessment	PANO/BTZ/DEX (n = 387)	PBO/BTZ/DEX (n = 381)	Statistical significance
PFS, months, median (95% CI)	11.99 (10.33 to 12.94)	8.08 (7.56 to 9.23)	HR, 0.63 95% CI, 0.52 to 0.76 p < 0.0001
OS,[a] months, median (95% CI)	33.64 (31.34, NE)	30.39 (26.87, NE)	HR, 0.87 95% CI, 0.69 to 1.10 p = 0.26
OS[b] months, median	38.24	35.38	HR, 0.87 95% CI, 0.70 to 1.07 p = 0.1783
ORR (at least PR), n (%, 95% CI)	235 (60.7, 55.7 to 65.6)	208 (54.6, 49.4 to 59.7)	p = 0.09
CR, n (%)	42 (11)	22 (6)	NA
nCR, n (%)	65 (17)	38 (10)	NA
PR, n (%)	128 (33)	148 (39)	NA
MR, n (%)	23 (6)	42 (11)	NA
No change, n (%)	65 (17)	74 (19)	NA
Progressive disease, n (%)	21 (5)	32 (8)	NA
Unknown, n (%)	43 (11)	25 (7)	NA
CR/nCR rate, % (95% CI)	27.6 (23.2 to 32.4)	15.7 (12.2 to 19.8)	p = 0.00006[c]
Duration of response, months, median (95% CI)	13.14 (11.76 to 14.92)	10.87 (9.23 to 11.76)	NA
Time to response, months (95% CI)	1.51 (1.41 to 1.64)	2.00 (1.61 to 2.79)	NA
Time to progression, months (95% CI)	12.71 (11.30 to 14.06)	8.54 (7.66 to 9.72)	NA

[a]Overall survival calculated from an interim analysis (10 September 2013, after 286 events, 69.0% complete)[9]

[b]Overall survival calculated from an interim analysis (18 August 2014, after 359 events, 86.5% complete)[25]

[c]*Post hoc* analysis.

BTZ, bortezomib; CI, confidence interval; CR, complete response; DEX, dexamethasone; HR, hazard ratio; MR, minimal response; NA, not analysed/assessed/available, nCR, near-complete response; NE, not evaluable; ORR,

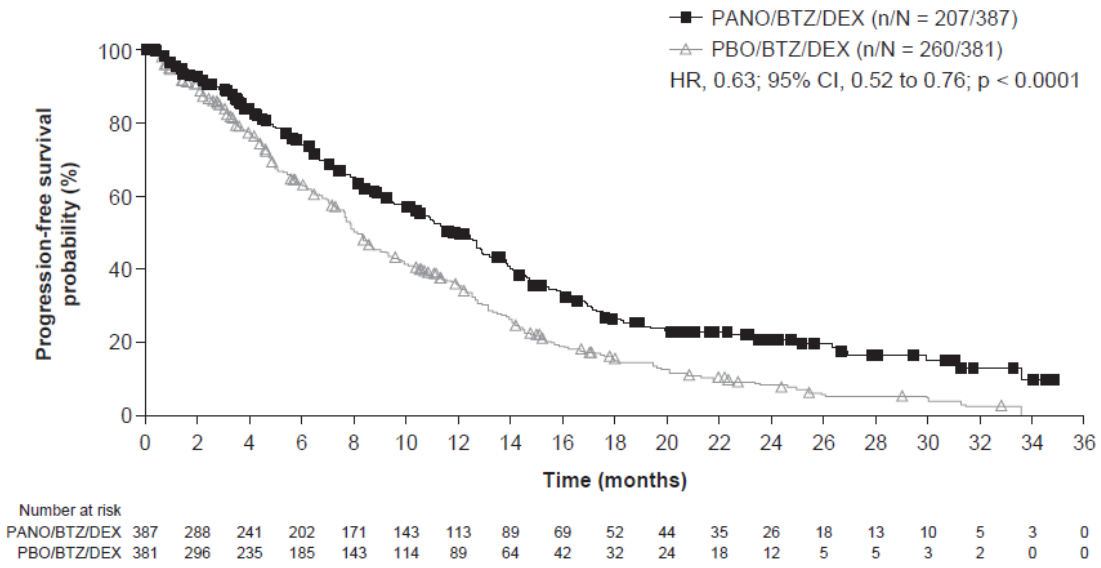
overall response rate; OS, overall survival; PANO, panobinostat; PBO, placebo; PFS, progression-free survival; PR, partial response.
FDA 2014[25]; San-Miguel et al., 2014[9].

4.7.2 Progression-free survival

Panobinostat plus BTZ/DEX provided a clinically meaningful extension of median progression-free survival to 12 months

In the final analysis, according to investigator assessment, median PFS was increased from 8.1 months for the control group to 12.0 months for the PANO/BTZ/DEX group; this was the primary endpoint for the study (11.99 months versus 8.08 months; $p < 0.0001$)[9]. Independent assessment of PFS also reported a statistically significant improvement for the panobinostat group (11.99 months versus 8.31 months; $p < 0{\cdot}0001$). The risk of progression was reduced by 37% in patients treated with PANO/BTZ/DEX versus patients treated with placebo/BTZ/DEX, according to both the investigator and the independent assessment (HR, 0.63; 95% CI, 0.52 to 0.76, $p < 0.0001$, Figure 11). A multivariate Cox model analysis adjusting for baseline characteristics, together with all other sensitivity analyses performed, further confirmed the PFS benefit for the panobinostat group over control (Table 13 and Table 14). A further analysis according to the number of prior lines of therapy indicated similar PFS benefits in patients who had received one or two prior lines of therapy (one prior line: HR, 0.69; 95% CI, 0.53 to 0.89; two prior lines: HR, 0.71; 95% CI, 0.51 to 1.01), and greater benefit in patients who had received three prior lines of therapy (HR, 0.46, 95% CI, 0.29, 0.72).

Figure 11 Progression-free survival in the PANORAMA-1 study (Kaplan–Meier analysis, full analysis set, data cut-off September 2013).



BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; PANO, panobinostat; PBO, placebo
San-Miguel et al,,2014[9]

Table 13 Sensitivity analysis for progression-free survival in the PANORAMA-1 study.

		PANO/BTZ/DEX (n = 381)	PBO/BTZ/DEX (n = 377)
PFS by investigator	PFS events, n (%)	207 (53.5)	260 (68.2)
	Censored, n (%)[a]	180 (46.5)	121 (31.8)
	Median time to event, months[b] (95% CI)	11.99 (10.32 to 12.94)	8.08 (7.56 to 9.23)
	Hazard ratio (95% CI) p value	0.63 (0.52 to 0.76) < 0.0001	
PFS by independent review	PFS events, n (%)	241 (62.3)	283 (74.3)
	Censored, n (%)	146 (37.7)	98 (25.7)
	Median time to event, months[b] (95% CI)	11.99 (10.51 to 13.50)	8.31 (7.62 to 9.92),
	Hazard ratio (95% CI) p value	0.63 (95% CI 0.52 to 0.76) < 0.0001	
Stratified Cox model adjusting for baseline characteristics[c]	PFS events, n	207	260
	Censored, n	180	121
	Median time to event, months[b] (95% CI)	11.99 (10.32 to 12.94)	8.08 (7.56 to 9.23)
	Hazard ratio (95% CI) p value	0.58 (0.48 to 0.71) < 0.0001	

[a]In the PFS analysis according to investigator assessment, 180 (46.5%) of the patients in the panobinostat group were censored compared with 121 (31.9%) in the placebo group. The main causes of censoring were lack of efficacy (22.2% panobinostat; 14.2% placebo), consent withdrawal (19% panobinostat; 11.8% placebo), > 2 missing assessments prior to event (9.3% panobinostat; 7.3% placebo), ongoing, in follow-up (9% panobinostat; 3.9% placebo), and new cancer therapy added (5.9% panobinostat; 6.3% placebo).

[b]Kaplan–Meier estimates.

[c]Baseline covariates included in the Cox proportional hazard model are: treatment group; age group; renal impairment; prior stem cell transplantation; clinical staging according to International Staging System, sex; race and geographic location; prior use of IMiDs; prior use of bortezomib (yes versus no); and number of prior therapies (1 versus 2/3).

Hazard ratio and 95% CI of PANO/BTZ/DEX versus PBO/BTZ/DEX are obtained from a stratified Cox model. The two-sided p value is obtained from the stratified log-rank test. p values for analyses other than the primary analysis are presented for descriptive purposes and for an assessment of the consistency and robustness of the primary analysis in terms of statistical significance.

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; IMiD, immunomodulatory drug; PANO, panobinostat; PBO, placebo; PFS, progression-free survival.

FDA 2014[25] San-Miguel et al.,2014[9]

Table 14 Additional sensitivity analysis for progression-free survival in the PANORAMA-1 study

	Median PFS, months		Hazard ratio (95% CI)
	PANO/BTZ/DEX (n = 381)	**PBO/BTZ/DEX (n = 377)**	
Per protocol investigator assessment	12.71 (11.04 to 14.06)	8.08 (7.13 to 9.69)	0.60 (0.49 to 0.75)
Per protocol independent review assessment	12.71	7.85	0.59 (0.48 to 0.74)
Patients without M-protein assessment	12.68	8.08	0.63 (0.51 to 0.78)

All analyses include a requirement for PD confirmation per mEBMT criteria

$p < 0.0001$ for all sensitivity analyses

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; mEBMT, modified European Group for Blood and Bone Marrow Transplant; PANO, panobinostat; PBO, placebo; PD, progressive disease; PFS, progression-free survival.

San Miguel et al 2014;[9] Data on file

Panobinostat plus BTZ/DEX provided meaningful gains in progression-free survival regardless of patient baseline characteristics and prior treatment

Analysis according to baseline characteristics revealed statistically significant improvements in PFS for the panobinostat group versus the control group for most pre-specified subgroups considered, including: patients who had relapsed and refractory disease; those with stage II to III disease; and those who were aged 65 years and older (Figure 12). Similarly, the statistical improvement in PFS was maintained regardless of prior treatment history, and was seen across all four randomisation strata (one prior line of therapy, two to three prior lines of therapy, prior treatment with bortezomib, and no prior bortezomib treatment) (Table 15).

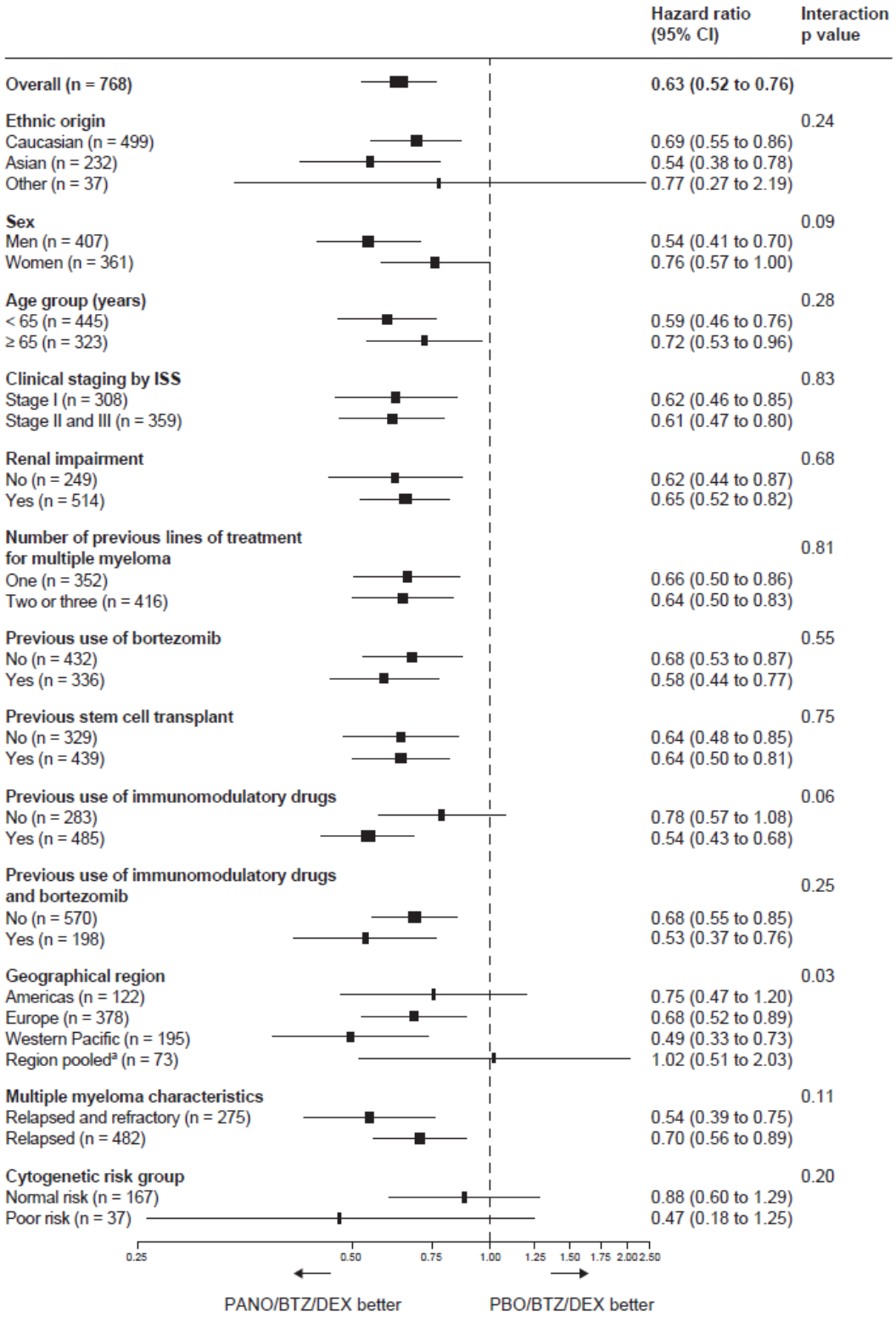
Table 15 Subgroup analysis for progression-free survival in the PANORAMA -1 study according to randomisation strata (full analysis set).

Subgroup	Event, %	Median PFS (95% CI), months	Cox model HR (95% CI), Log-rank p value
All patients			
PANO/BTZ/DEX	53.5	11.99 (10.32 to 12.94)	0.63 (0.52 to 0.76)
PBO/BTZ/DEX	68.2	8.08 (7.56 to 9.23)	
One prior line of therapy			
PANO/BTZ/DEX	54.5	12.25 (9.46 to 14.62)	0.66 (0.50 to 0.86)
PBO/BTZ/DEX	70.7	8.54 (7.72 to 10.41)	
Two or three prior lines of therapy			
PANO/BTZ/DEX	52.6	11.99 (9.46 to 13.70)	0.64 (0.50 to 0.83)
PBO/BTZ/DEX	66.2	7.62 (6.01 to 8.67)	
Prior BTZ use			
PANO/BTZ/DEX	58.0	11.04 (8.34 to 13.70)	0.58 (0.44 to 0.77)
PBO/BTZ/DEX	68.9	7.56 (5.88 to 7.89)	
No prior BTZ use			
PANO/BTZ/DEX	50.0	12.48 (10.18 to 14.16)	0.68 (0.53 to 0.87)
PBO/BTZ/DEX	67.8	8.64 (7.98 to 10.84)	

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; PANO, panobinostat; PBO, placebo; PFS, progression-free survival.

Data on file[105]

Figure 12 Subgroup analysis for progression-free survival in the PANORAMA-1 study (full analysis set).



BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; ISS, International Staging System; PANO, panobinostat; PBO, placebo.

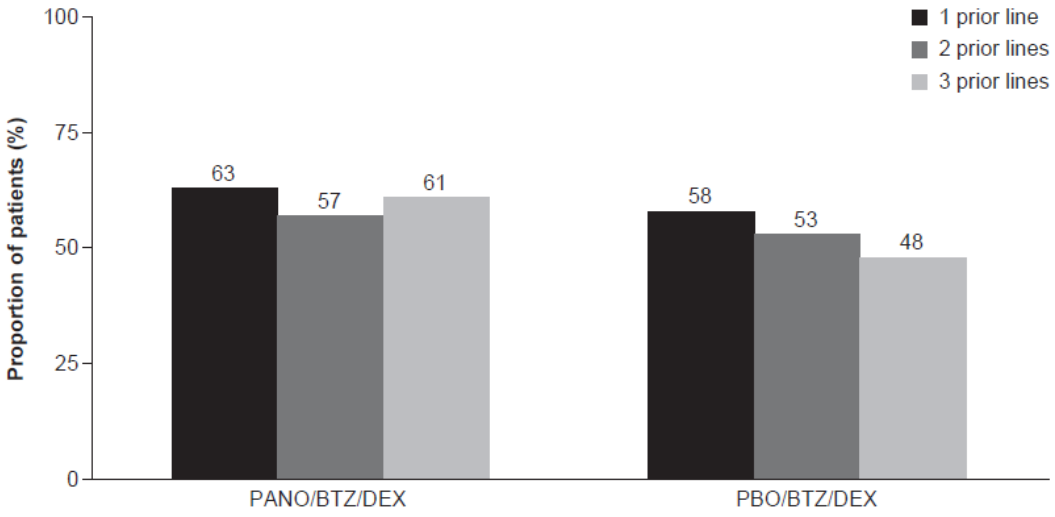
San-Miguel et al.,2014[9]

4.7.3 Response

Panobinostat improved the time to response and the quality of response to treatment when combined with bortezomib and dexamethasone, regardless of the number of prior lines of therapy

The ORR did not differ significantly between treatment groups (PANO/BTZ/DEX, 60.7%; placebo/BTZ/DEX, 54.6%; p = 0.09). However, in the PANO/BTZ/DEX group ORR was consistent, regardless of number of prior lines of treatment, unlike in the control arm (Figure 13).

Figure 13 Overall response rate in the PANORAMA-1 study according to number of prior lines of therapy



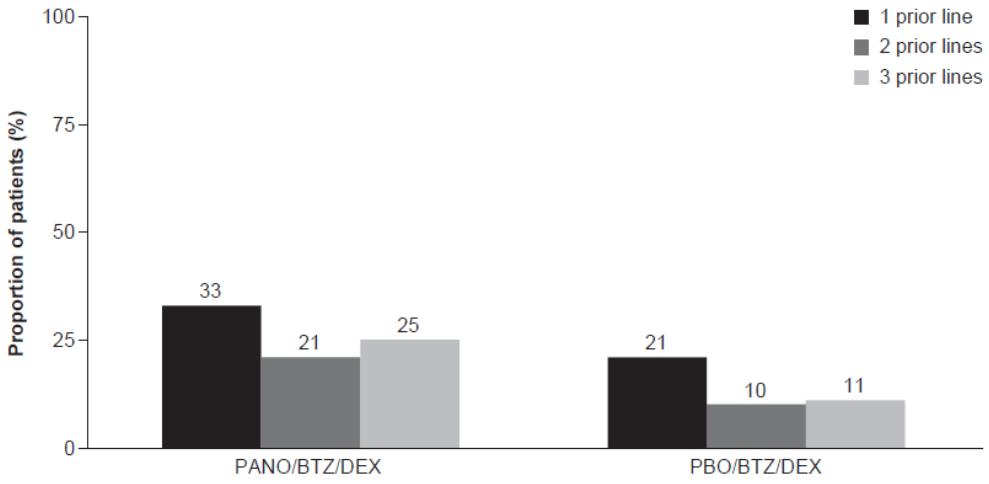
ORR assessed according to mEBMT criteria

BTZ, bortezomib; DEX, dexamethasone; mEBMT, modified European Group for Blood and Bone Marrow Transplant; PANO, panobinostat; PBO, placebo.

Data on file

Furthermore, the proportion of patients achieving a CR or nCR was approximately two-fold higher in the PANO/BTZ/DEX group than in the placebo/BTZ/DEX group (27.6% versus 15.7%; p = 0.00006, Table 12), and this difference was observed across the three subgroups with respect to number of prior therapies (Figure 14).

Figure 14 CR/nCR rate in the PANORAMA-1 study according to number of prior lines of therapy



CR/nCR assessed according to mEBMT criteria

BTZ, bortezomib; CR, complete response; DEX, dexamethasone; mEBMT, modified European Group for Blood and Bone Marrow Transplant; nCR, near-complete response; PANO, panobinostat; PBO, placebo.

Data on file

Consistent with this, according to a landmark analysis of data from PANORAMA-1, deeper responses (CR/nCR versus PR) were associated with a longer median PFS in both treatment groups for each time point evaluated (Table 16).

Table 16 Landmark analysis for PFS response according to response status in the PANORAMA-1 study

Landmark time and treatment group	Number of patients		Median PFS after landmark time, months		HR (95% CI)
	with CR/nCR	with PR	Patients with CR/nCR	Patients with PR	
6 weeks					
PANO/BTZ/DEX	12	57	NE	12.55	0.33 (0.12 to 0.89)
PBO/BTZ/DEX	3	57	15.80	10.18	0.85 (0.19 to 3.90)
12 weeks					
PANO/BTZ/DEX	49	107	16.49	10.32	0.40 (0.25 to 0.65)
PBO/BTZ/DEX	23	122	14.13	9.69	0.62 (0.36 to 1.07)
18 weeks					
PANO/BTZ/DEX	76	104	16.49	10.94	0.43 (0.29 to 0.65)
PBO/BTZ/DEX	41	126	14.55	10.41	0.54 (0.35 to 0.82)
24 weeks					
PANO/BTZ/DEX	84	96	18.96	11.99	0.40 (0.27 to 0.59)
PBO/BTZ/DEX	46	112	14.88	11.76	0.57 (0.38 to 0.87)

Analysis performed for the full analysis set and response determined according to EBMT criteria. Stratified Cox model used to obtain HR and 95% CI

BTZ, bortezomib; CI, confidence interval; CR, complete response; DEX, dexamethasone; EBMT, European Group for Blood and Bone Marrow Transplant; HR, hazard ratio; nCR, near-complete response; PANO, panobinostat; PBO, placebo; PFS, progression-free survival; PR, partial response.

Data on file[149,150]

Complete or near complete responses achieved with PANO/BTZ/DEX were associated with almost 4 months longer PFS than that achieved for a similar level of response with BTZ/DEX.

Patients who achieved a CR/nCR with PANO/BTZ/DEX experienced a 4-month longer PFS than those who achieved a similar level of response with BTZ/DEX. This may be related to the synergism between panobinostat and bortezomib (see section 2.1) leading to a longer duration of response. Consistent with this, the median duration of response (≥ PR) was prolonged in the PANO/BTZ/DEX group (13.14 months) compared with the placebo/BTZ/DEX group (10.87 months), whereas median time to response (≥ PR) was similar for both groups (PANO/BTZ/DEX, 1.51 months; placebo/BTZ/DEX, 2.00 months). Similar results were observed when analysed separately for patients achieving a CR/nCR or achieving a PR (Table 17). Furthermore, within each treatment group the duration of response is significantly longer in patients achieving a CR/nCR compared with those achieving only a PR.

Significant difference was seen between the duration of CR/nCR versus duration of PR on both treatment arms. Also there was significant difference in the duration of response between the two treatment arms as long as CR/nCR was reached benefiting PANO/BTZ/DEX

Table 17 Time to response and duration of response in patients achieving a PR or CR/nCR in the PANORAMA-1 study

	Time to response (95% CI), months		**Duration of response (95% CI), months**	
	PANO/BTZ/DEX (n = 381)	**PBO/BTZ/DEX (n = 377)**	**PANO/BTZ/DEX (n = 381)**	**PBO/BTZ/DEX (n = 377)**
Patients achieving ≥ PR according to investigator assessment	1.51 (1.41 to 1.64)	2.00 (1.61 to 2.79)	13.14 (11.76 to 14.92)	10.87 (9.23 to 11.76)
Patients achieving CR/nCR according to investigator assessment	0.76 (0.76 to 0.95)	0.76 (0.72 to 0.82)	18.43 (15.18 to 25.56)	14.52 (13.40 to 18.04)
Patients achieving PR according to investigator assessment	1.41 (0.95 to 1.45)	1.41 (1.41 to 1.51)	9.00 (7.62 to 11.20)	8.77 (6.97 to 10.61)

Analysis performed for the full analysis set and response determined according to EBMT criteria

BTZ, bortezomib; CI, confidence interval; CR, complete response; DEX, dexamethasone; EBMT, European Group for Blood and Bone Marrow Transplant; nCR, near-complete response; PANO, panobinostat; PBO, placebo; PR, partial response.
San Miguel 2014;[9] Data on file

Responses in the control group were consistent with those seen in previous studies.[13,20]

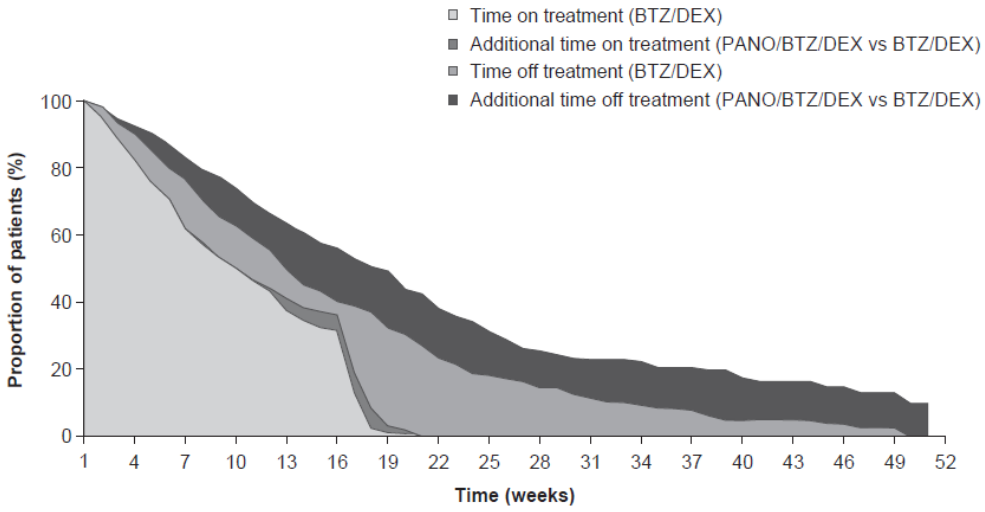
4.7.4 Treatment-free interval

Patients benefited from a 94% increase in the duration of the Treatment Free Interval when treated with PANO/BTZ/DEX compared with BTZ/DEX

In the PANORAMA-1 trial the *median* duration of treatment was shorter in the panobinostat group than in the placebo group (5·0 months [interquartile range, IQR 2·23 to 10·75] versus 6·1 months [2·82 to 10·75]), whereas median PFS achieved with PANO/BTZ/DEX (11.99 months) was longer than in the control group (8.08 months). This thus suggests that PANO/BTZ/DEX provided a significantly longer TFI.

The *mean* duration of treatment, however, was similar for both treatment groups (PANO/BTZ/DEX, 6.63 months; placebo/BTZ/DEX, 6.46 months, full analysis set). Despite this, the mean time a patient remained treatment-free up to progression was longer in the PANO/BTZ/DEX group, 7.49 months (95% CI:6.05 to 8.55) compared with only 3.86 months (95% CI: 3.09 to 4.65) in the control group (Figure 15).

Figure 15 Time on treatment and treatment-free interval for overall population in the PANORAMA-1 study

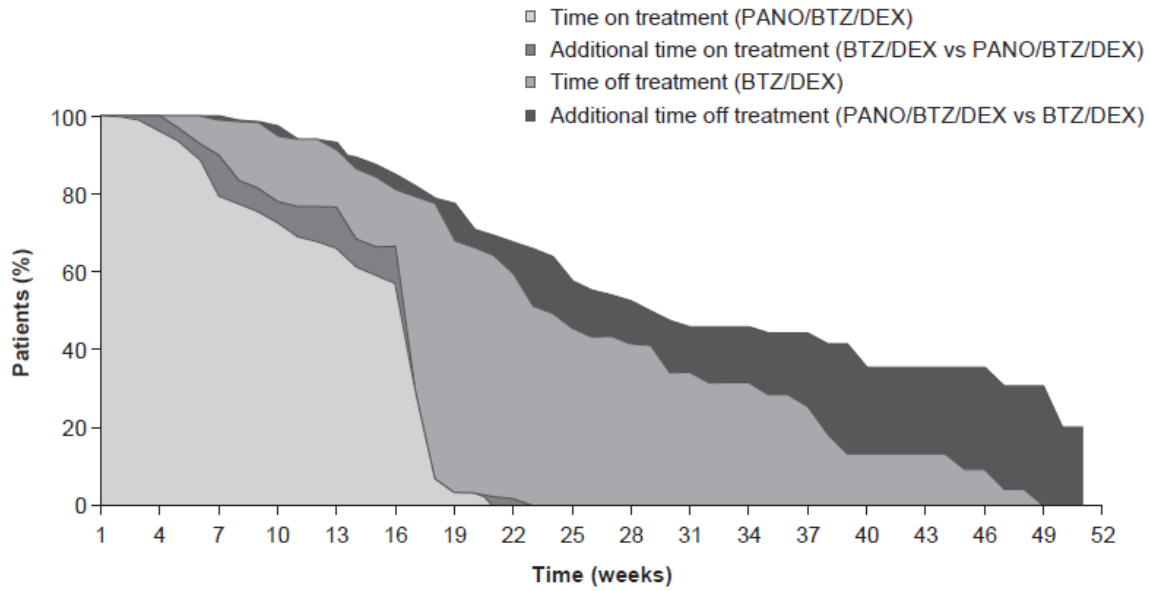


BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.
Data on file[92]

The longer PFS observed in the PANO/BTZ/DEX group could be related to the quality of the observed responses that were more favourable in the PANO/BTZ/DEX group compared to the placebo/BTZ/DEX group, as evidenced the higher rate of nCR/CR (27.6% versus 15.7%).

The difference in the TFI between treatment groups was even more marked for patients who achieved a CR/nCR; in these patients TFI was 8.39 months for patients randomised to placebo/BTZ/DEX compared with 12.92 months for the panobinostat group, an extension of 4.53 months (Figure 16).

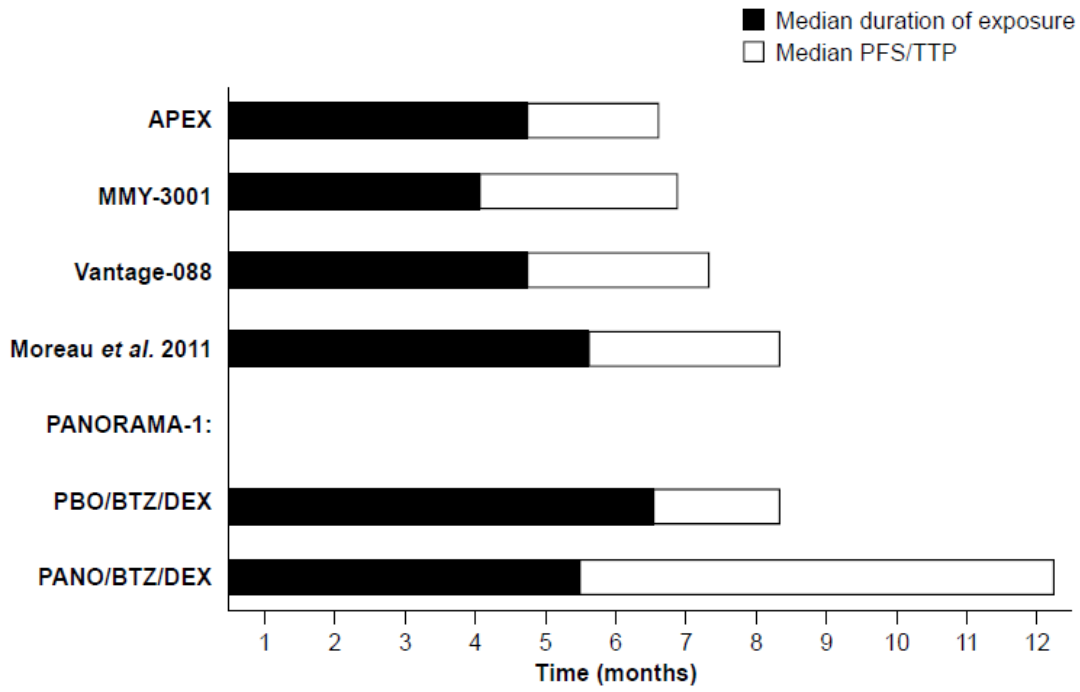
Figure 16 Time on treatment and treatment-free interval for patients achieving a CR/nCR in the PANORAMA-1 study



BTZ, bortezomib; CR, complete response; DEX, dexamethasone; nCR, near-complete response; PANO, panobinostat.
Data on file[92]

The duration of exposure to BTZ/DEX and the associated PFS in the control group were consistent with those seen in previous studies (Figure 17).

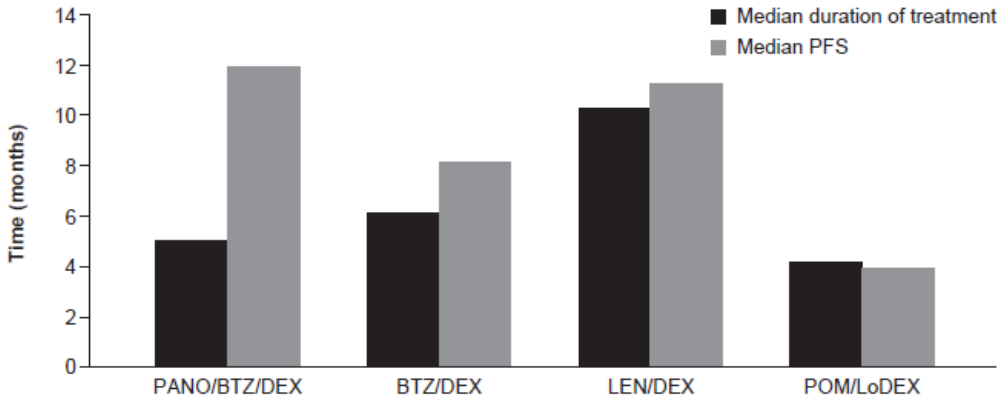
Figure 17 Duration of exposure and TTP/PFS reported in various trials with bortezomib



APEX: TTP, 6.22 months; DoT, 4.14 months. MMY-3001: TTP, 6.5 months; DoT, 3.45 months. Vantage-088: PFS, 7.63 months; DoT, 4.14 months. Moreau-2011: PFS, 8.00 months; DoT, 5.52 months. PANORAMA-1, PBO: PFS, 8.08 months; DoT, 6.1 months. PANORAMA-1, PANO: PFS, 11.99 months; DoT, 5.0 months
BTZ, bortezomib; DEX, dexamethasone; DoT, duration of treatment; PANO, panobinostat; PFS, progression-free survival; TTP, time to progression.
APEX, Richardson et al 2005 & 2007; [12,20] MMY-3001, Orlowski et al 2007;[21] Vantage-088, Dimopoulos et al 2013;[22] Moreau et al 2011[13]

Current treatment guidance for the management of MM suggests therapy should aim to achieve a period of stable disease for as long as possible by maximising duration of response as well as maximising HRQL.[52] As discussed in section 3.2, a number of studies have shown that HRQL scores alter according to line of treatment and are improved at times when disease is in remission and patient are off treatment, ie during the TFI between lines of therapy. Furthermore, a longer TFI is associated with a better HRQL.[23] With the current standards of care, other than following a stem cell transplantation, the duration of the TFI achieved can be limited, as discussed in section 3.7 (see Figure 18 and Figure 6).

Figure 18 Duration of exposure and TTP/PFS reported in various trials with current standard of care novel agents



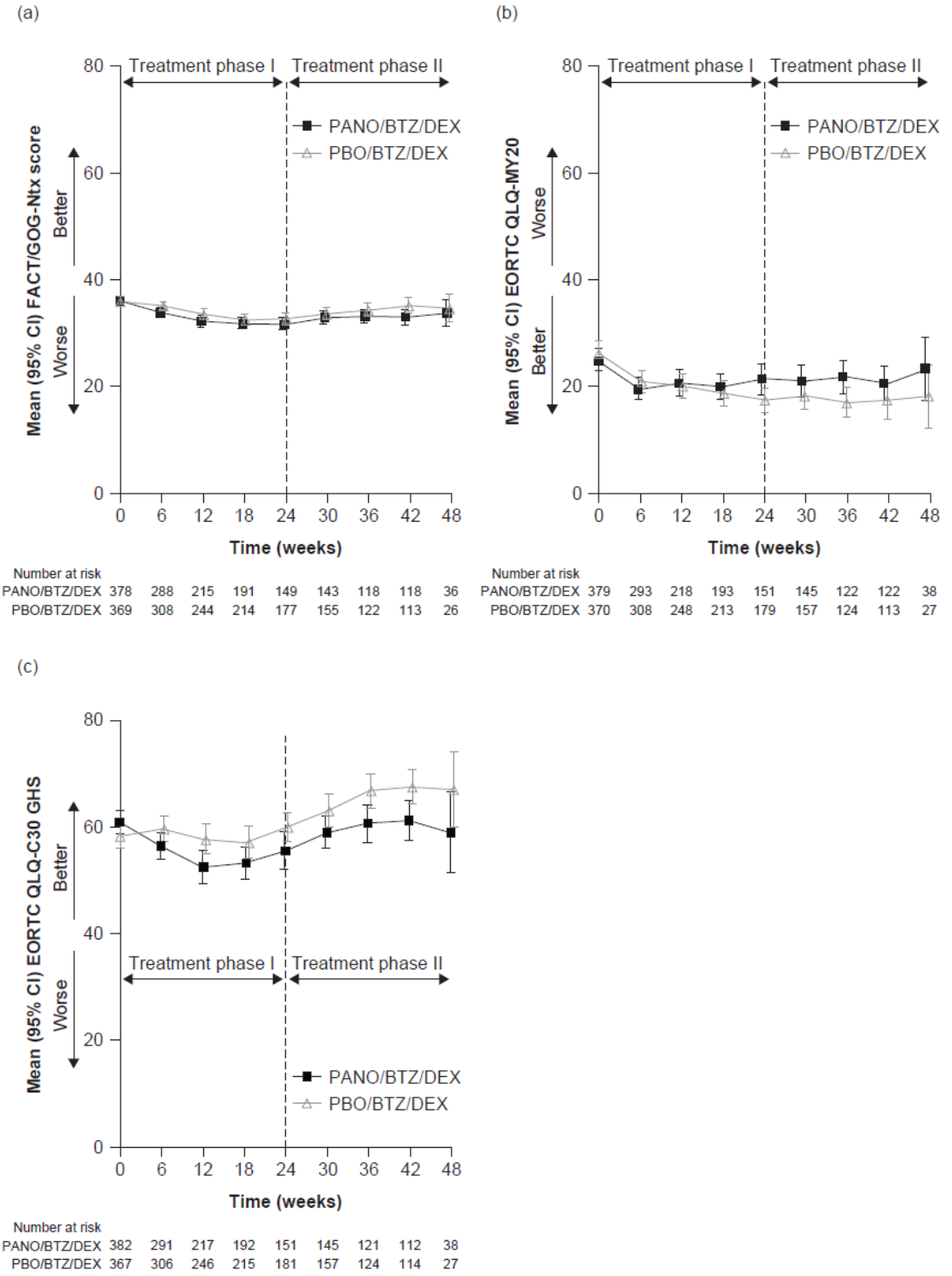
BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; LoDEX, low dose dexamethasone; PANO, panobinostat; PFS, progression-free survival; POM, pomalidomide; TTP, time to progression.
San Miguel 2014;[9] Dimopolous et al 2007;[95] Celgene 2014;[106] San Miguel et al 2013;[94] Siegel et al 2013[107]

4.7.5 HRQL

Panobinostat triplet therapy was associated with an improvement in symptoms and global HRQL improved after an initial decline over the first 4 cycles of therapy

HRQL was assessed during treatment until disease progression or treatment discontinuation. Scores for neurotoxicity, assessed using the FACT FACT/GOG-Ntx neurotoxicity subscale, were similar in both treatment groups, suggesting no difference in symptoms of peripheral neuropathy, while scores for myeloma-specific disease symptoms showed an initial improvement (decline in values) in both groups followed by stabilization (Figure 19).[25] Results for the EORTC QLQ-C30 GHS score showed an initial decrease in HRQL up to week 12 (ie the end of cycle 6), followed by an improvement towards baseline values for the second treatment period during which patients remaining on study received bortezomib less frequently.

Figure 19 Scores for a) neurotoxitiy and b) disease-related symptoms during treatment and c) HRQL (Global Health Status) with panobinostat triplet therapy versus control in the PANORAMA-1 study

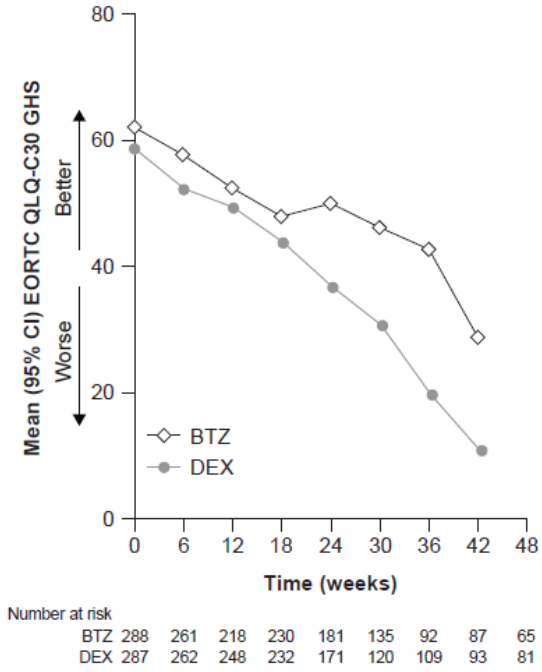


BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – C30; EORTC QLQ-MY20, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module;

FACT/GOG-Ntx, Functional Assessment of Cancer Therapy Gynecologic Oncology Group – neurotoxicity; GHS, Global Health Status; HRQL, health-related quality of life; PANO, panobinostat; PBO, placebo.
FDA 2014;[25]

This contrasts with EORTC QLQ-C30 GHS scores reported for bortezomib in the pivotal APEX trial,[108] where HRQL declined markedly during treatment with bortezomib or dexamethasone (Figure 20). This may reflect the gain in clinical experience with management of the adverse events associated with bortezomib over the years since the approval of bortezomib.

Figure 20 HRQL (Global Health Status) scores for bortezomib and dexamethasone in the APEX trial



BTZ, bortezomib; DEX, dexamethasone; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – C30; GHS, Global Health Status; HRQL, health-related quality of life.
Lee et al. 2008[108]

Panobinostat triplet therapy can be expected to improve HRQL for patients with rrMM when considered over the entire period from initiation of panobinostat therapy to subsequent disease progression

In the PANORAMA-1 study HRQL was not assessed during the TFI. As discussed in section 3.2, a survey of UK patients has reported that HRQL is improved in patients during the TFI compared with during active treatment and that prolongation of the TFI is associated with an improvement in HRQL.[23] Given that, compared with BTZ/DEX, panobinostat prolonged the TFI by a mean of 3.63 months in the overall population and by 4.53 months in patients achieving a CR/nCR, panobinostat triplet therapy can be expected to improve HRQL when considered over the period from initiation of therapy

for rrMM to initiation of subsequent therapy on disease progression. This benefit however has been estimated using a modelling approach (see section 5.4 for more details) and suggests that in the overall patient population, patients receiving panobinostat triplet therapy gain 0.53 quality-adjusted life year (QALY) over patients receiving BTZ/DEX. This reflects the improved HRQL experienced during the TFI, estimated to be 0.51 (panobinostat triplet therapy) versus 0.21 (BTZ/DEX) QALY (see section 5.7.1).

4.7.6 Overall survival

A numerical improvement in overall survival was observed for panobinostat triplet therapy over BTZ/DEX

OS data have been reported for the 10 September 2013 data cut-off (first pre-planned interim analysis; corresponding to the final analysis for PFS) and for a data cut-off of 18 August 2014 (second interim analysis). Although the survival data from both analyses are not mature, both suggest a consistent numerical survival advantage for the panobinostat group (Table 18). The final analysis will be done after 415 deaths have been recorded.

Table 18 Analysis of overall survival for first and second interim analyses

	PANO/BTZ/DEX (n = 387)	**PBO/BTZ/DEX (n = 381)**	**HR (95% CI),[a] p-value[b]**
First pre-planned interim analysis, 10 September 2013 data cut-off			
OS events, n (%)	134 (34.6)	152 (39.9)	0.87 (0.69 to 1.10), p = 0.2586
Censored, n (%)	253 (65.4)	229 (60.1)	
Kaplan–Meier estimates (95% CI), months at: 25th percentile probability 75th percentile probability	 16.49 (13.63 to 20.47) NE	 15.21 (13.08 to 17.91) NE	
Median OS, (95% CI), months	33.64 (31.34 to NE)	30.39 (26.87 to NE)	
Second interim analysis, 18 August 2014 data cut-off			
OS events, n (%)	169 (43.7)	190 (49.9)	0.87 (0.70 to 1.07) p = 0.1783
Censored, n (%)	218 (56.3)	191 (50.1)	
Kaplan–Meier estimates (95% CI), months at: 25th percentile probability 75th percentile probability	 16.49 (14.55 to 21.26) NE	 15.18 (13.08 to 17.48) NE	
Median OS, (95% CI), months	38.24 (34.63 to 45.37)	35.38 (29.37 to 39.92)	

[a]Hazard ratio (HR) is obtained from stratified Cox model.

[b]2-sided p-value is obtained from the stratified log-rank test.

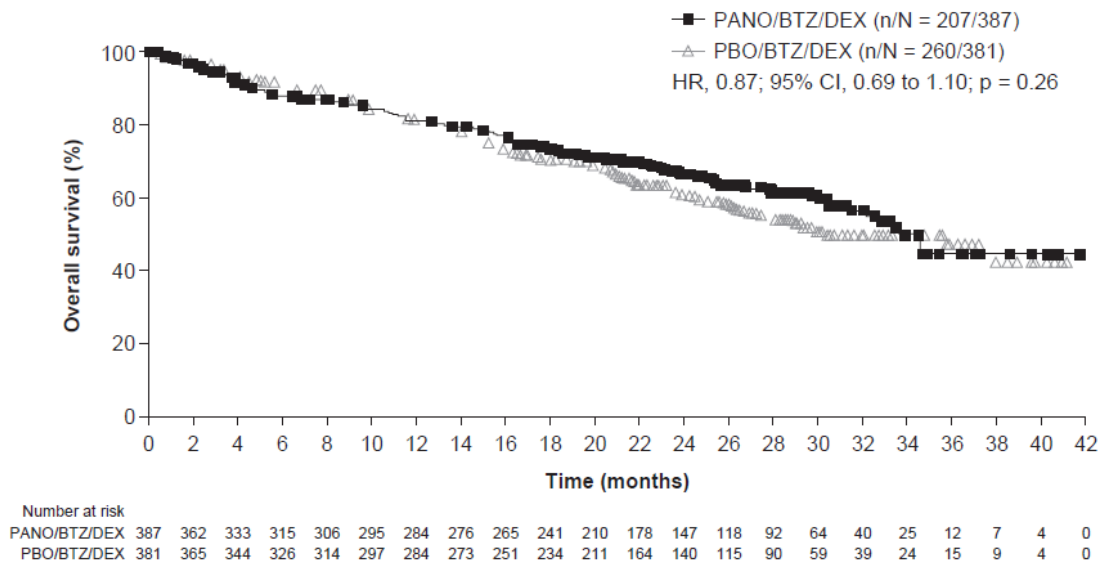
BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; NE, not estimable; OS, overall survival; PANO, panobinostat; PBO, placebo;

FDA 2014[25] Data on file

At data cut-off of September 2013, 286 deaths had occurred (134 [35%] in the panobinostat group and 152 [40%] in the placebo group), and median OS was 33.64 months (95% CI 31·34 to not estimable) in the panobinostat group versus 30·39 months (26.87 to not estimable) in the placebo group (HR 0.87, 95% CI 0.69 to 1·10; p = 0.26; Figure 21).[9]

As of the August 2014 data cut-off, 359 (86.5%) of the target 415 OS events had occurred: 169 in the panobinostat group and 190 in the control group. Of the 409 censored patients, 342 continued to be observed for survival data. Median OS was 38.24 months for the panobinostat group and 35.38 months for the control group (p = 0.1783) (Figure 22). Panobinostat triplet therapy was associated with a 13% reduction in the risk of death versus BTZ/DEX (HR, 0.87; 95% CI, 0.70 to 1.07).

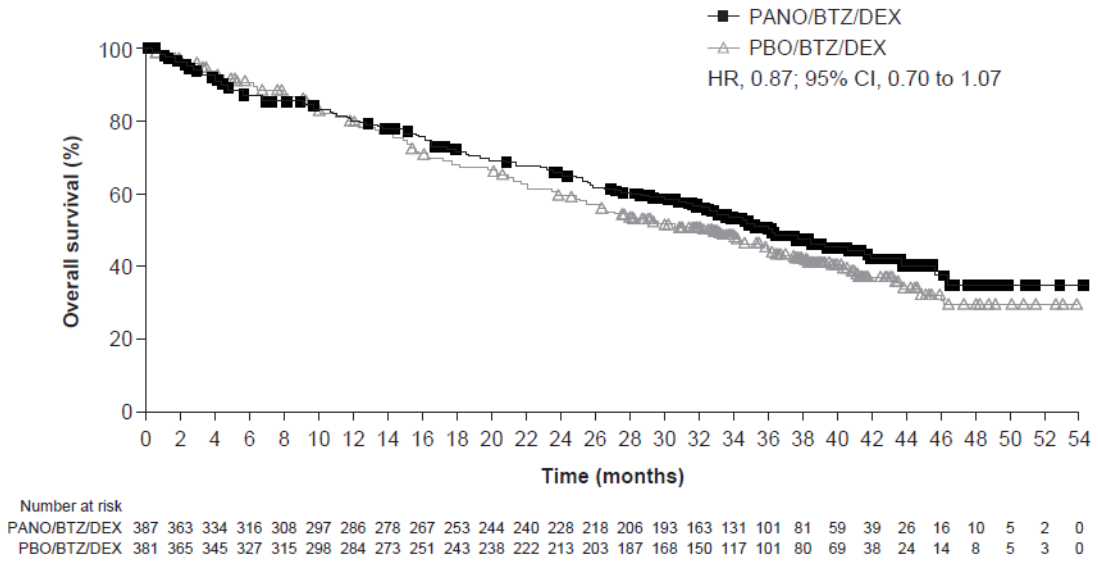
Figure 21 Kaplan–Meier curve for overall survival in the PANORAMA-1 study (full analysis set, 1st interim analysis).



BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; PANO, panobinostat; PBO, placebo.

San Miguel et al 2014[9]

Figure 22 Kaplan–Meier curve for overall survival in the PANORAMA-1 study (full analysis set, 2nd interim analysis).



BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; OS, overall survival; PANO, panobinostat; PBO, placebo.

FDA, 2014[25]

4.8 Subgroup analysis

As discussed in section 4.7.2, the effect of the addition of panobinostat to BTZ/DEX on PFS was confirmed by sensitivity analyses and was consistent across all stratification factors and subgroups analysed for PANORAMA-1, suggesting benefit irrespective of previous treatment or baseline characteristics.[9] HRs within all major subgroups were consistently in favour of the panobinostat group, indicating that benefits were seen independent of age, sex, race, prior therapies (ie, bortezomib, IMiDs, stem cell transplantation), renal impairment, clinical staging by International Staging System, relapsed or relapsed and refractory disease, and cytogenetic risk.[9,25]

One of the most relevant factors regarding the choice of therapy for patients with rrMM is the mechanisms of action of the therapies patients have previously received. At present, as the most active compounds used in MM are PIs and IMiDs, it is essential to characterize to which of these two classes of compounds patients have become refractory, as one of the main features impacting response to future treatments. Patients who fail after receiving both classes of drugs generally have a poor outcome, thus underscoring the importance of introducing drugs with new mechanisms of action.

Further efficacy and safety analyses were therefore performed for two subgroups differentiated by the type and the number of prior lines of treatment, ie patients who had received prior IMiD plus bortezomib (n = 193, 25% of the study population), and patients who had received prior IMiD plus bortezomib and ≥ 2 prior lines of treatment (n = 147, 19% of the study population) and an additional

subgroup with 2 to 3 prior lines of treatment (n = 371, 48.3% of the study population). Table 19 summarises the efficacy and safety data for these subgroups compared with the overall study population.

Table 19 Efficacy and safety data for PANORAMA-1 according prior treatment compared with overall study population

	Overall study population		Prior IMiD and BTZ		Prior IMiD plus BTZ and ≥ 2 prior lines of treatment,		2-3 prior lines of treatment	
	PANO/ BTZ/DEX N = 387/381	PBO/ BTZ/DEX N = 381/377	PANO/ BTZ/DEX N = 94/92	PBO/ BTZ/DEX N = 99/99	PANO/ BTZ/DEX N = 73/72	PBO/ BTZ/DEX N = 74/73	PANO/ BTZ/DEX N = 188/186	PBO/ BTZ/DEX N = 183/182
Median PFS, months HR (95% CI)	12.0 0.63 (0.52 to 0.76) p < 0.0001	8.1	10.6 0.52 (0.36 to 0.76) p = 0.0005	5.8	12.5 0.47 (0.32 to 0.72)	4.7	11.30 0.61 (0.46 to 0.80)	7.56
Median OS, months HR (95% CI)	38.2 0.87 (0.70 to 1.07) p = 0.1783	35.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORR, % (95% CI)	60.7, (55.7 to 65.6)	54.6, (49.4 to 59.7)	58.5 (47.9 to 68.6), p = 0.019	41.4 (31.6 to 51.8)	58.9 (46.8 to 70.3)	39.2 (28.0 to 51.2)	58.5 (51.1 to 65.6)	50.8 (43.3 to 58.3)
CR/nCR, % (95% CI)	27.6 (23.2 to 32.4) P = 0.00006	15.7 (12.2 to 19.8)	22.3 (14.4 to 32.1)	9.1 (4.2 to 16.6) P = 0.012	21.9 (13.1 to 33.1)	8.1 (3.0 to 16.8)	22.3 (16.6 to 29.0)	10.4 (6.4 to 15.7)
Median duration of response, months	13.14 (11.76 to 14.92)	10.87 (9.23 to 11.76)	12.0	8.3	11.99 (9.69 to 13.37)	6.97 (4.86 to 13.40)	N/A	N/A
Median TTP	12.71 (11.30 to 14.06)	8.54 (7.66 to 9.72)	12.3	6.1	12.68 (8.34 to 14.19)	4.99 (3.75 to 6.80)	N/A	N/A
On-treatment deaths, %	7.9	4.8	6.4	5.1	6.9	6.8	N/A	N/A

Grade 3/4 AEs, %								
Thrombocytopaenia	67.4	31.4	66.3	46.5	68	44	69.4	35.7
Infections (pneumonia)	15.7	12.7	18.5	14.1	19.4	16.4	18.3	14.3
Infections (sepsis)	6.6	3.7	4.3	5.1	2.8	6.8	3.8	5.5
Diarrhoea	25.5	8.3	30.4	13.1	33.3	15.1	33.3	9.9
Asthenia/Fatigue	23.9	11.9	25.0	12.1	26.4	13.7	25.3	11.5
Haemorrhage	4.2	2.4	3.3	2.0	2.8	2.7	4.3	1.1
Neutropenia	34.5		27.2	10.1	31.9	9.6	n/a	n/a

AE, adverse event; BTZ, bortezomib; CI, confidence interval; CR, complete response; DEX, dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; nCR, near-complete response; ORR, overall/objective response rate; OS, overall survival; PANO, panobinostat; PBO, placebo. PFS, progression-free survival; TTP, time to progression FDA 2014[25]; San-Miguel et al., 2014[9]; Data on file[151,152,153]

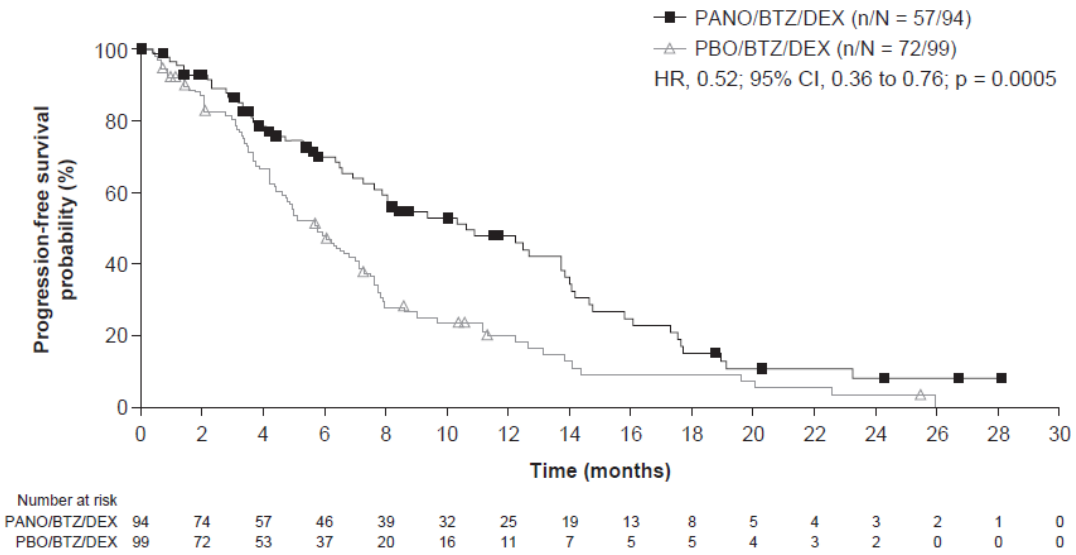
4.8.1 Prior IMiD plus bortezomib subgroup

Patients who had received prior IMiD plus bortezomib therapy was one of the pre-specified subgroups considered in the analysis of PANORAMA-1 given that therapeutic options for patients who have failed both IMiDs and bortezomib is very limited. This subset of patient (n = 193) constituted 25% of the total study population and the cohort had more advanced disease compared to the overall study population; a higher proportion of patients had relapsed-and-refractory disease (51% versus 36%), and the median time from initial diagnosis to enrollment in the study was longer (45 and 40 months in the prior bortezomib and IMiD subset versus 37 and 39 months in the overall population, respectively in the panobinostat and control groups). Furthermore, this subset of patients was more heavily pretreated having received a median of two prior therapies compared with one for the overall study population, and 76.1% of patients had received ≥ 2 prior lines of treatment. A higher proportion of patients had received previous stem cell transplantation (71%) in comparison to the overall study population (57.2%).

Patients who had received prior IMiD and bortezomib therapy achieved a greater benefit with PANO/BTZ/DEX over BTZ/DEX compared with the overall study population

The benefit achieved with PANO/BTZ/DEX over BTZ/DEX in this subgroup was greater than that observed in the overall study population. PFS was prolonged by a clinically meaningful 4.8 months (from 5.8 months to 10.6 months) with the addition of panobinostat to BTZ/DEX demonstrating a 48% risk reduction in PFS in favour of treatment with PANO/BTZ/DEX (HR, 0.52; 95% CI: 0.36 to 0.76; p = 0.0005, Figure 23). Although interim OS data for the overall population are still immature, median OS in the panobinostat group was numerically higher than in the control group ([redacted] months versus [redacted] months, Figure 24) in this patient subgroup at the last interim OS analysis which was performed after 86.5% of the targeted 415 OS events in the overall population had occurred (data cut-off, August 2014). The addition of panobinostat to BTZ/DEX was also associated with a higher ORR and CR/nCR, and a longer median duration of response and TTP compared with the control group (Table 19).

Figure 23 Progression-free survival in the PANORAMA-1 study for patients who had received prior IMiD and bortezomib therapy (Kaplan–Meier analysis, full analysis set, data cut-off September 2013).



BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; PANO, panobinostat; PBO, placebo.

Data on file[151,154]

Figure 24 Kaplan–Meier curve for overall survival in the PANORAMA-1 study for patients who had received prior IMiD and bortezomib therapy (full analysis set, 2nd interim analysis).

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; PANO, panobinostat; PBO, placebo.

Data on file[153]

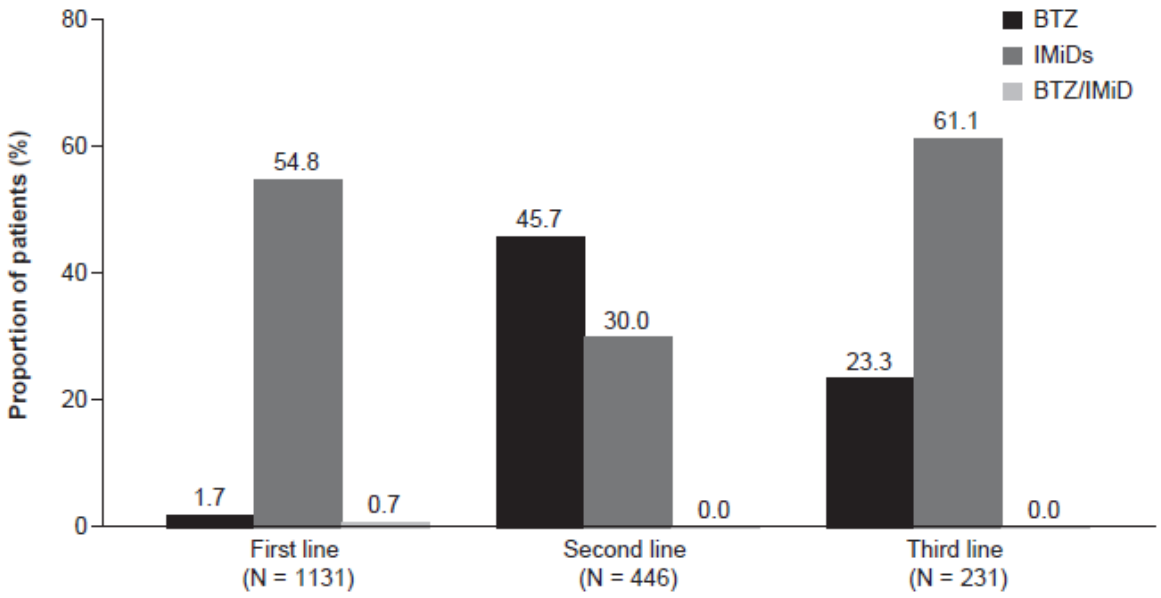
The relative risk of experiencing adverse events revealed a more favourable safety profile for PANO/BTZ/DEX in patients who had received prior IMiD and bortezomib, compared with the overall study population

The safety profile of the PANO/BTZ/DEX in this subgroup of patients was generally consistent with that in the overall population or slightly more favourable. In the control group, there was a higher rate of grade 3/4 thrombocytopenia (48%), and grade 3/4 infections (pneumonia: 14%; sepsis: 5%) in the subset of patients with prior bortezomib and IMiDs as compared to the subset of patients who have not received prior bortezomib and IMiDs, consistent with a more heavily-treated population and patients having more advanced disease. The number of on-treatment deaths was comparable between the two treatment groups (panobinostat, n = 6, 6.5%; control, n = 5, 5.1%) of which 0% and 2%, respectively, were attributed to disease progression. An analysis of the relative risk of experiencing adverse events in the panobinostat group versus the control group revealed a more favourable safety profile in patients who had previously received IMiD and bortezomib compared with the total study population, as reflected in lower relative risks of on-treatment deaths (subgroup, 1.3; overall population, 1.7), thrombocytopenia (subgroup, 1.4; overall population, 2.2), diarrhoea (subgroup, 2.3; overall population, 3.1) and sepsis (subgroup, −0.9; overall population, 1.8).

4.8.2 Prior IMiD plus bortezomib and at least two prior lines of treatment

In the UK, most patients receive an IMiD and bortezomib as separate lines of therapy. For example, data from the HMRN audit for a cohort of patients over the period from 2003 to 2011 indicates that only 0.7% of patients received an IMiD plus bortezomib as first-line therapy and no patients received this combination as second-line therapy (Figure 25). Despite the fact that some aspects of management of MM have changed over the last 4 years since this audit, this observation is consistent with current recommendations; the draft National Chemotherapy Algorithm v.7[79] only recommends IMiD plus bortezomib combination therapy for transplant eligible patients prior to the first ASCT (in line with NICE TA311, see section 3.3), while the BCSH guidelines[51] mention the possibility of use of this combination in the induction setting, but do not include this combination among their recommendations. Thus in the UK most patients who have previously received therapy with an IMiD and bortezomib have received at least two prior lines of therapy. This was also the case for the patient population included in the PANORAMA-1 trial where 76.1% of patients who had received prior therapy including an IMiD and bortezomib had received at least two lines of therapy.

Figure 25 Use of bortezomib and IMiDs in first-, second- and third-line in English patients



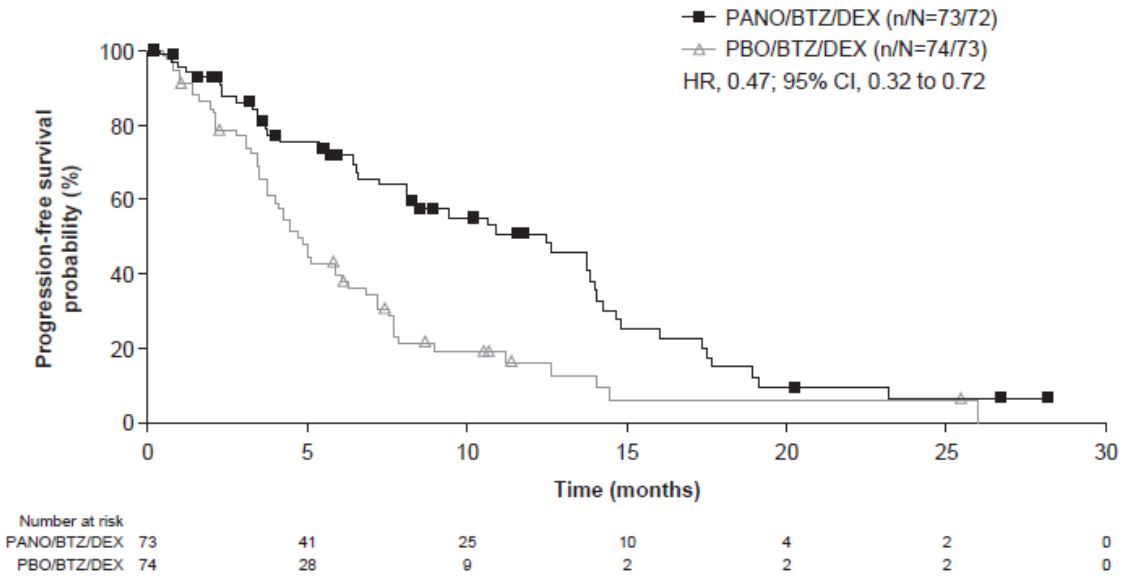
BTZ, bortezomib; IMiD, immunomodulatory drug.

HMRN 2015[60]

The addition of panobinostat to BTZ/DEX prolonged median PFS by nearly 8 months in patients who had received prior IMiD and bortezomib therapy and were receiving third-line or later therapy

In the PANORAMA-1 trial, 147 patients had received prior IMiD plus bortezomib and ≥ 2 prior lines of treatment, constituting 19% of the study population. The efficacy outcomes for this subgroup demonstrate a comparable or even greater benefit (compared to the IMiD plus bortezomib subgroup) for the addition of panobinostat to BTZ/DEX as summarised in Table 19. Median PFS was extended by 7.8 months, representing a 53% reduction in the risk of progression, and OS was extended by [redacted] months from [redacted] months to [redacted] months (Figure 26 and Figure 27). Increases in the ORR and CR/nCR with PANO/BTZ/DEX over the control group were similar to those observed in the prior IMiD plus bortezomib subgroup. The incidence of grade 3/4 adverse events was consistent with that observed in the prior IMiD plus bortezomib subgroup. While not a pre-specified subgroup in the study protocol, this subgroup analysis was requested by the FDA corresponds to the indication approved by the FDA.[35]

Figure 26 Progression-free survival in the PANORAMA-1 study for patients who had received prior IMiD and bortezomib therapy and at least two lines of therapy (data cut-off September 2013).



BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; PANO, panobinostat; PBO, placebo.
Data on file[151]

Figure 27 Kaplan–Meier curve for overall survival in the PANORAMA-1 study for patients who had received prior IMiD and bortezomib therapy and at least two lines of therapy (2nd interim analysis).

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; PANO, panobinostat; PBO, placebo.
Data on file[151]

4.9 Meta-analysis

No meta-analysis was undertaken. Only a single RCT was identified.

4.10 Indirect and mixed treatment comparisons

Other than the PANORAMA-1 study, no direct head-to-head trials have compared panobinostat triplet therapy with regimens used in the management of patients with rrMM. An indirect treatment comparison using the common comparators method was therefore performed to provide evidence for the efficacy of PANO/BTZ/DEX relative to other regimens used in this setting. The results of this analysis have been presented at the Annual meeting of the American Society of Hematology (ASH) in December 2014.[109] However, this methodology has certain limitations and hence two further approaches were also used to provide inputs for the economic assessment.

For the economic analysis, data for the relative efficacy of PANO/BTZ/DEX versus LEN/DEX is required as LEN/DEX is a relevant comparator for panobinostat triplet therapy in the management of rrMM in the third-line setting or later (see section 3.3) Two alternative approaches were used to provide comparative efficacy data for PANO/BTZ/DEX and LEN/DEX:

- Comparison of efficacy outcomes (median PFS and OS) for the treatment arms of interest in relevant trials without any adjustment for differences in design between the trials (ie a naïve comparison)
- Comparison of efficacy outcomes using matching adjusted indirect treatment comparison (MAIC) methodology.

CTD (Cyclophosphamide/THAL/DEX) is another possible comparator for consideration in the third-line setting or later (according to the NICE scope) but is not widely used in the UK; according to the HMRN audit CTD was used in only 10% of patients in the third-line or fourth-line setting.[60] Furthermore, the National Chemotherapy Algorithm[79] does not recommend CTD as an option in the third or fourth-line setting. Nevertheless, relevant clinical evidence to allow comparison of CTD with panobinostat in the third-line setting or later were sought.

4.10.1 Search strategy

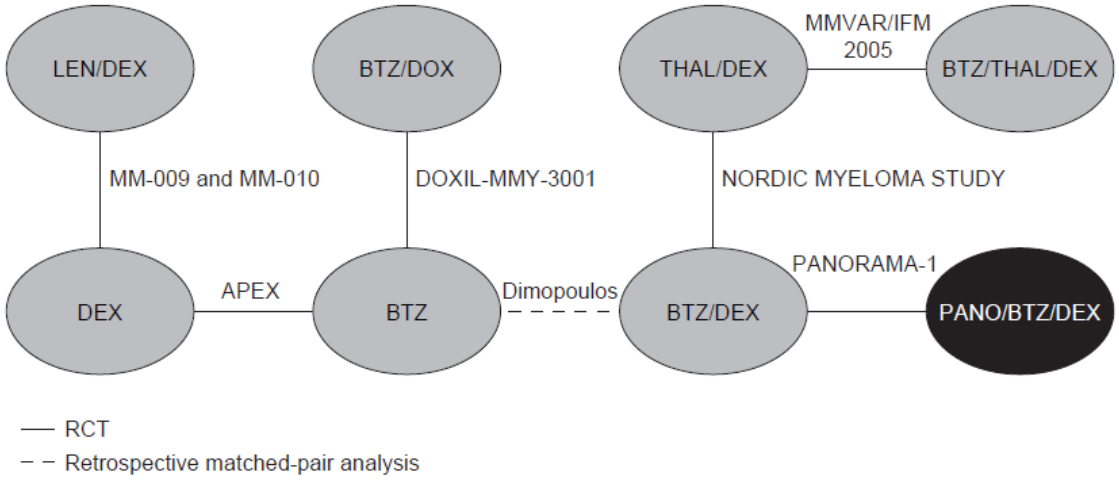
As described in section 4.1 and Appendix 2, a systematic literature review was performed to identify relevant evidence for the three indirect treatment comparisons. Comparators considered were regimens including bortezomib, thalidomide, lenalidomide, dexamethasone, and pegylated liposomal doxorubicin (DOX). Selected publications included those reporting the results for phase 2 to 4 clinical trials specifically focusing on rrMM and reporting results in English. Searches were performed in MEDLINE, MEDLINE In-Process, Embase, the Cochrane Library, and conference proceedings were searched, covering clinical studies dating from January 2003 to April 2014.

4.10.2 Study selection

Common comparators method

For the indirect treatment comparison using the common comparators method, multi-arm RCTs that could be linked via common comparators were selected for inclusion in the preliminary evidence base of the indirect treatment comparison and created the network shown in Figure 28. These trials were assessed in terms of trial design (eg, patient selection criteria) and patient characteristics (eg, age, time since diagnosis, number of prior lines of therapy). As a result of the assessment, two trials identified for the preliminary evidence network were excluded from the final network. These studies together with the rationale for exclusion are summarised in Table 20. Furthermore, the values for TTP for THAL/DEX reported for the two excluded trials differed considerably from each other (MMVAR/IFM-2005 trial, 13.8 months; Nordic Myeloma Study, 9.8 months).

Figure 28 Preliminary evidence network



BTZ, bortezomib; DEX, dexamethasone; DOX, doxorubicin; LEN, lenalidomide; PANO, panobinostat; PBO, placebo; RCT, randomised controlled trial; THAL, thalidomide.

Table 20 Rationale for exclusion of two studies from the final network

Study/Reference	Comparison	Rationale for exclusion
NORDIC MYELOMA study[110]	THAL/DEX versus BTZ/DEX	1) Included patients must have been refractory to melphalan 2) THAL/DEX is not considered a valid comparator in the UK as it is not included in the draft Chemotherapy Algorithm (v.7),[79] or the BCSH Guidelines[51] 3) In the HMRN audit no patients received THAL/DEX as third or fourth-line therapy.[60]
MMVAR/IFM-2005[111]	BTZ/THAL/DEX (ie VTD) versus THAL/DEX	1) The trial involved patients who had progressed or relapsed after one ASCT and it must have been their first relapse 2) The draft (v.7) Chemotherapy Algorithm[79] recommends use of VTD as an induction treatment prior to SCT in line with NICE TA331.[85] 3) NICE Guidelines (TA129, TA228)[52,88] exclude the use of THAL/BTZ 4) THAL/DEX is not considered a valid comparator in the UK as it is not included in the draft Chemotherapy Algorithm (v.7),[79] or the BCSH Guidelines[51]

ASCT, autologous stem cell transplantation; BCSH, British Committee for Standards in Haematology; BTZ, bortezomib; DEX, dexamethasone; HMRN, Haematological Malignancy Research Network; NICE, National Institute for Health and Care Excellence; SCT, stem cell transplant; THAL, thalidomide; VTD, bortezomib, thalidomide and dexamethasone

Naive comparison and MAIC

RCTs reporting the efficacy and safety of LEN/DEX were selected for use in a naïve comparison and MAIC to provide evidence for the efficacy of LEN/DEX versus panobinostat triplet therapy in the third-line and later settings after prior IMiD and bortezomib. These methodologies can also be applied to single-arm studies. As no RCTs investigating CTD in relevant patients populations were identified, single-arm studies were also considered.

4.10.3 Methods and outcomes of included studies

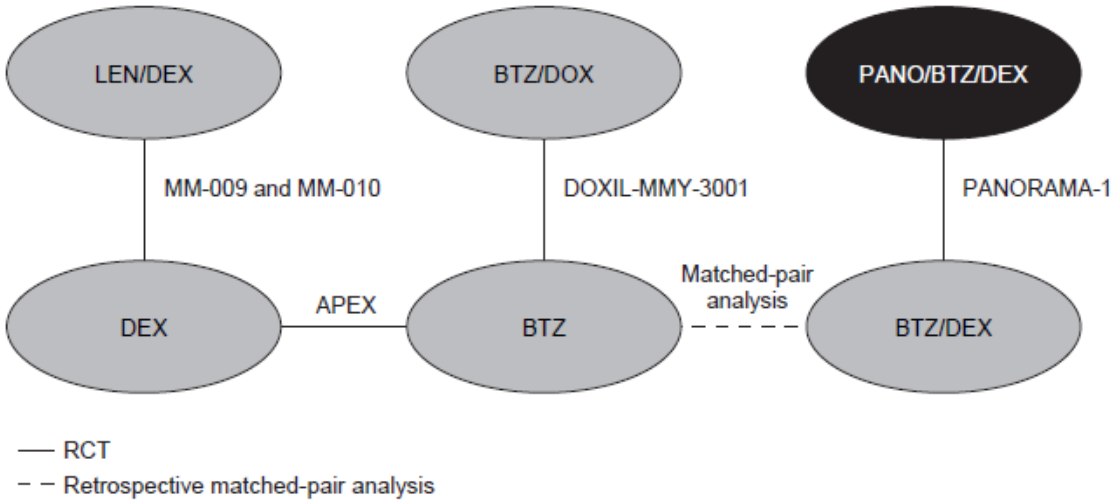
Common comparators method

Data were derived from five published multi-arm RCTs in patients with rrMM. In addition, results of a retrospective matched-pairs comparison analysis using propensity score matching was used to provide evidence for the efficacy of BTZ/DEX versus dexamethasone because no clinical trial was identified for this comparison. The final evidence network (Figure 29) was based on the following controlled clinical trials:

- PANORAMA-1, the pivotal phase 3 study for panobinostat (n = 768), provides data for PANO/BTZ/DEX versus BTZ/DEX.[9]
- Pooled data from the MM-009 and MM-010 trials, the two pivotal phase 3 studies for lenalidomide (n = 704) provide data for LEN/DEX versus dexamethasone.[95,112,113]
- DOXIL-MMY-3001, a phase 3 study assessing the benefit of the addition of doxorubicin (n = 646), provides data for BTZ/DOX versus bortezomib.[21]

- APEX, the pivotal phase 3 trial for bortezomib (n = 669), provides data for bortezomib versus high-dose dexamethasone.[20]
- A retrospective matched-pair analysis of data for 218 patients provides data for BTZ/DEX versus bortezomib.[114]

Figure 29 Evidence network for the common comparator method



BTZ, bortezomib; DEX, dexamethasone; DOX, doxorubicin; LEN, lenalidomide; PANO, panobinostat; RCT, randomised controlled trial.

The selected trials were similar in terms of trial design (eg patient selection criteria). Baseline patient characteristics were similar in terms of median age (61 to 64 years), disease duration (24 to 48 months at baseline), and proportions of patients with one prior line of therapy (32% to 46%), except for the matched pairs analysis, where only patients with one prior line of therapy were considered (Table 21). A total of 3005 patients were included in the studies. The proportions of patients receiving each regimen were as follows: PANO/BTZ/DEX, 13%; BTZ/DEX, 16%; bortezomib, 25%; dexamethasone, 23%; LEN/DEX; 12%, BTZ/DOX, 11%. Overall, based on the assessment of the trials, it was concluded that these trials are sufficiently similar to be included in an evidence network and to serve as a basis for the indirect treatment comparison. No statistical assessment of heterogeneity was conducted because except for LEN/DEX there was only one trial per treatment available.

Naïve comparison and MAIC

Pooled data and subpopulation analysis data from the MM-009 and MM-010 trials, the two pivotal phase 3 studies for lenalidomide, provided data for LEN/DEX for use in the naïve comparison and

MAIC..[95,112,113,155] A total of 353 patients received LEN/DEX in these two studies; baseline characteristics are described in Table 21.

One single-arm study investigating CTD in the relevant patient population was identified.[115] This study involved 53 patients. Median PFS and duration of treatment were not reported for this study and the patient characteristics differ significantly from those of patients involved in PANORAMA-1, eg 88% of patients had received more than 3 lines of prior therapy (compared with no patients in PANORAMA-1) and most were naïve for thalidomide (81%) compared with 47% in PANORAMA-1. Given the small patient population (n = 53) and the significant differences in baseline characteristics compared with PANORAMA-1 it was deemed inappropriate to perform a naïve comparison or MAIC. It was therefore decided not to include CTD as a comparator in the economic assessment given that few patients receive this regimen in the third-line setting or later in the UK.[60]

Table 21 Baseline characteristics of patients in the trials included in the indirect treatment comparisons

	PANORAMA -1		**Matched Pairs Analysis**		**APEX**		**MM-009**		**MM-010**		**DOXIL MMY-3001**	
	PANO/ BTZ/DEX N = 387	BTZ/DEX N = 381	BTZ/ DEX N = 109	BTZ N = 109	BTZ N = 333	DEX N = 336	LEN/DEX N = 177	DEX N = 176	LEN/DEX N = 176	DEX N = 175	BTZ /DOX N = 324	BTZ N = 322
Age, median, years	63	63	62	64	62	61	64	62	63	64	61	62
Male, %	52.2	53.8	–	–	56.5	59.5	59.9	59.1	59.1	58.9	58.3	54.0
Time since diagnosis, Median, months	37.1	38.9	32.4	24	42	37.2	37.2	37.2	40.8	48.0	35.2	37.5
ECOG performance 0, %	45.2	42.5	24.0	23.0	–	–	41.8	47.2	44.3	37.1	43.0	45.2
ECOG performance 1, %	49.4	48.8	65.0	67.0	–	–	46.9	45.5	40.9	45.1	57.0	54.8
1 Prior line of therapy, %	46.0	45.7	100	100	39.8	35.4	38.4	38.1	31.8	32.6	33.6	34.2
≥ 2 Prior lines of therapy, %	54.0	54.3	–	–	60.2	64.6	61.6	61.9	68.2	67.4	66.4	65.8
Prior thalidomide therapy, %	53.0	49.3	–	–	48.2	50.0	41.8	45.5	30.1	38.3	–	–
Prior bortezomib therapy	43.7	42.3	–	–	–	–	10.7	11.4	4.5	4.0	–	–
Prior stem cell transplant, %	55.6	58.8	40.0	47.0	66.9	68.2	61.6	61.4	55.1	54.3	57.4	53.7

[a] Dashes indicate where data were not available or applicable

BTZ, bortezomib; DEX, dexamethasone; DOX, doxorubicin; ECOG, Eastern Cooperative Oncology Group; LEN, lenalidomide; PANO, panobinostat.

Dimopoulos et al.,2007;[95]Dimopoulos et al.,2009;[112] Orlowski et al.,2007:[21] Richardson et al.,2005;[20] San-Miguel et al.,2014;[9] Weber et al.,2007;[113]

4.10.4 Methods of analysis and presentation of results

Table 22 summarises the three different methodologies used for the indirect treatment comparisons.

Table 22 Summary of the methods used for indirect treatment comparison and the advantage and disadvantages of the methodologies as used in this analysis

	Common comparators method	**Naive comparison**	**Unadjusted Cox regression**	**Matching adjusted indirect treatment comparison (Cox regression)**
Comparators considered	BTZ/DEX, BTZ, DEX, LEN/DEX, BTZ/DOX	LEN/DEX	LEN/DEX	LEN/DEX
Study population employed in the comparison	ITT population	ITT population; 2 to 3 prior lines of treatment	ITT population; 2 to 3 prior lines of treatment	ITT population; 2 to 3 prior lines of treatment
Adjustment to patient population differences	Implicitly assumes that relative efficacy measures are comparable	No adjustment for patient characteristics	No adjustment for patient characteristics	PANORAMA-1 population was adjusted to the MM-009/010 populations in terms of patient selection and baseline patient/ disease characteristics
Data type used	Aggregate data	Aggregate data	• Patient level data (PANO/BTZ/DEX) • Simulated patient level data for OS and PFS (LEN/DEX)	• Patient-level data (PANO/BTZ/DEX) • Simulated patient level data for OS and PFS (LEN/DEX) • Aggregate data for baseline characteristics (LEN/DEX)
Advantages of the methodology	Established methodology	Simple and transparent	• Use of patient level data • Patient numbers are not affected by matching	• Can adjust for baseline characteristics including relative treatment effect modifiers • By matching patient populations this approach mimics randomisation
Disadvantage	• Assumes factors that may influence the	• No randomisation	• Assumes proportional hazard assumption which	• Does not adjust for unobserved differences

	relative treatment effect (eg, HR) are balanced across the trials in the evidence network • May be large uncertainty around the outcomes as observed in this case for LEN/DEX versus PANO/BTZ/DEX)	• No adjustment to differences in patients or in trial design between studies	may not be true	between trials • Matching performed only for shared variables • Assumes proportional hazard assumption which may not be true
Outcomes compared (relative efficacy measure)	• PFS (HR) • TTP (HR) • CR/nCR (OR) • OS (HR)	• PFS (HR) • OS (HR)	• PFS (HR) • OS (HR)	• PFS (HR) • OS (HR)
Context applied in health economic model	• Third line treatment	• Third line treatment	• Third line treatment	• Third line treatment

BTZ, bortezomib; CR, complete response; DEX, dexamethasone; DOX, doxorubicin; HR, hazard ratio; ITT, Intention-to-treat; LEN, lenalidomide; nCR, near-complete response; OR, odds ratio; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; TTP, time to progression.

Common comparators method

This approach followed the established principles of an indirect treatment comparison,[116] ie relying on the randomisation within each trial that compared the treatments directly, and using the relative effect measures for the analyses. This method thus separates the true efficacy of a drug from possible placebo effects.

Data from the systematic literature review were analysed by applying fixed-effects models to estimate HRs of PFS, TTP, and OS and the odds ratio of CR/nCR. PANO/BTZ/DEX was chosen as the reference treatment for ease of comparison of the results and their interpretation. Only aggregate data were used for the primary analyses. Table 23 summarises the data used in the indirect treatment comparison.

Table 23 Summary of data used in the indirect treatment comparison (common comparators method)

Study	Arm 1	Arm 2	No of patients (Arm1 /Arm 2)	HR of PFS	HR of TTP	No of patients with CR or nCR (Arm1 /Arm2)	HR of OS
PANORAMA-1[a]	PANO/ BTZ/DEX	BTZ/ DEX	387/381	0.630[b]	0.602[b]	107/60	0.87
Matched-pairs analysis	BTZ/DEX	BTZ	109/109	0.595	0.394[b]	11/9	0.958
APEX[a]	BTZ	DEX	315/312	0.550[b]	0.550[b,c]	41/5	0.570
MM-009[*]	DEX	LEN/ DEX	177/176	2.970[b]	2.822[b]	3/43	0.440
MM-010[*]	DEX	LEN/ DEX	176/175	2.567[b]	2.850[b]	9/43	0.660
DOXIL-MMY-3001[*,a]	BTZ	BTZ/ DOX	324/322	1.690[b]	1.820[b]	33/42	1.410

* The inverse of the hazard ratio (control arm versus experimental arm) was reported.

[a] BTZ was administered intravenously in the studies.

[b] $p < .05$.

[c] HR not reported; assumed to be the same as HR of TTP.

BTZ, bortezomib; CR, complete response; DEX, dexamethasone; DOX, doxorubicin; HR, hazard ratio; LEN, lenalidomide; nCR, near-complete response; OS, overall survival ; PANO, panobinostat; PFS, progression-free survival; TTP, time to progression

Dimopoulos et al.,2007;[95]Dimopoulos et al.,2009;[112] Orlowski et al.,2007:[21] Richardson et al.,2005;[20] San-Miguel et al.,2014;[9] Weber et al.,2007;[113]

The models were conducted using Markov chain Monte Carlo simulation methods implemented in WinBUGS 1.4.[117] Vague priors were imposed and 360,000 iterations were run with the first 60,000 iterations being discarded. Every 30th simulation was retained to ensure independence between the simulations. The mean of the posterior distribution was taken as the point estimate, and 95% credible intervals (ie, ranges of values containing the true mean with a probability of 95%) were calculated.

Table 24 summarises the results of the indirect treatment comparison.

Table 24 Summary of the results of the indirect treatment comparison (common comparators method)

	PANO/BTZ/DEX	BTZ/DEX	BTZ	DEX	LEN/DEX	BTZ/DOX
PFS HR (± CrI)[a]	1.00	1.60 (1.32 to 1.92)	2.77 (1.54 to 4.62)	5.11 (2.51 to 9.20)	1.87 (0.87 to 3.49)	1.66 (0.87 to 2.90)
TTP HR (± CrI)[b]	1.00	1.67 (1.37 to 2.01)	2.92 (1.60 to 4.95)	5.40 (2.62 to 10.00)	1.91 (0.90 to 3.60)	1.61 (0.83 to 2.85)
CR/nCR (± CrI)[c]	1.00	0.50 (0.34 to 0.69)	0.44 (0.14 to 1.04)	0.05 (0.01 to 0.15)	0.49 (0.08 to 1.63)	0.60 (0.17 to 1.51)
OS (± CrI)[d]	1.00	1.15 (0.91 to 1.45)	1.25 (0.65 to 2.19)	2.23 (1.03 to 4.16)	1.22 (0.53 to 2.39)	0.91 (0.42 to1.72)

[a] Values > 1 indicate shorter PFS than for PANO/BTZ/DEX.

[b] Values > 1 indicate shorter TTP than for PANO/BTZ/DEX.

[c] Values < 1 indicate lower rate of CR + nCR than for PANO/BTZ/DEX.

[d] Values > 1 indicate shorter OS than for PANO/BTZ/DEX.

BTZ, bortezomib; CR, complete response; CrI, credible interval; DEX, dexamethasone; DOX, doxorubicin; HR, hazard ratio; LEN, lenalidomide; nCR, near-complete response; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; TTP, time to progression.

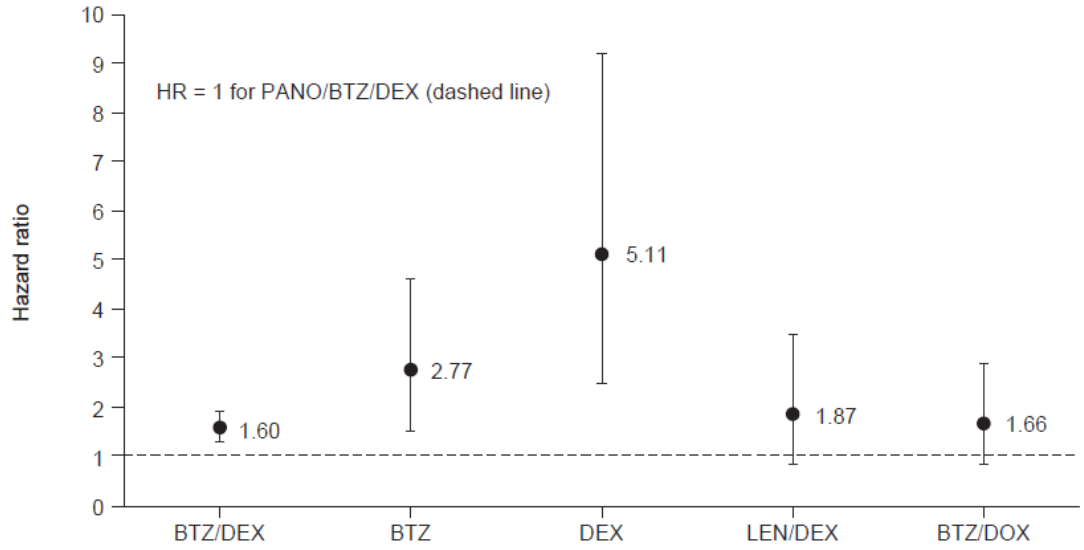
Richardson et al 2014[109]

Panobinostat is at least as efficacious as other treatments in rrMM and provides significant advantages against most comparators

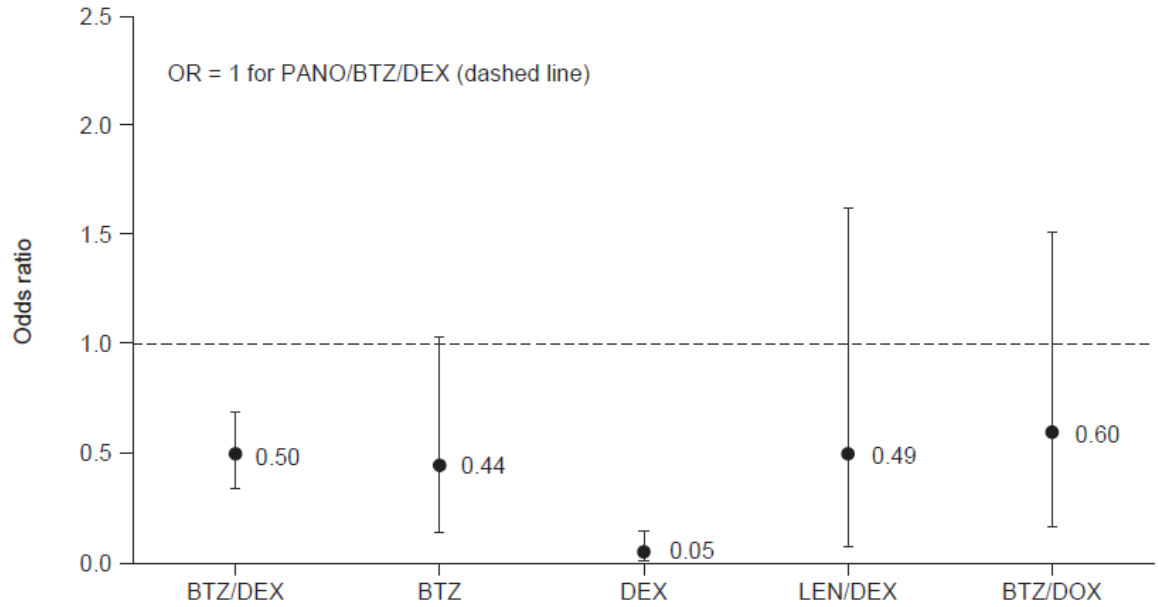
In this comparison, PANO/BTZ/DEX triplet therapy shown to be superior to all five comparator regimens for PFS, TTP and CR/nCR and differences were statistically significant except versus LEN/DEX and BTZ/DOX (Figure 30). For all three outcomes considered, the smallest statistically significant difference was obtained for PANO/BTZ/DEX compared to BTZ/DEX. As discussed in section 4.7.6 OS data are not yet mature for the PANORMA-1 trial. Nevertheless, the analysis indicated a more favourable OS for PANO/BTZ/DEX for all comparators except for BTZ/DOX, although differences were not statistically significant except against dexamethasone monotherapy. Thus within the recognised limitations of this type of analysis, the numerical trends reported here suggest that PANO/BTZ/DEX is at least as efficacious as other treatments in rrMM and provides significant advantages against most comparators.

Figure 30 Hazard ratios on progression-free survival and b) odds ratios on CR/nCR rates for each treatment in comparison to panobinostat triplet therapy

a)



b)



Values > 1 for HR indicate PFS advantage for PANO/BTZ/DEX against its comparators. The error bars represent the 95% CrIs corresponding with the HR.

Values < 1 for OR indicate CR + nCR advantage for PANO/BTZ/DEX against its comparators. The error bars represent the 95% CrIs corresponding with the OR.

BTZ, bortezomib; CR, complete response; CrI, credible interval; DEX, dexamethasone; DOX, doxorubicin; HR, hazard ratio; LEN, lenalidomide; nCR, near-complete response; OR, odds ratio; PANO, panobinostat; PFS, progression-free survival.

Richardson et al. 2014[109]

Naïve comparison of PANO/BTZ/DEX versus LEN/DEX

This naïve comparison was performed for PFS and OS outcomes based on the comparison of the median PFS and OS estimates of the corresponding trials (ie MM-009/010[112,155] and PANORAMA-1).[25]

Results of the naïve comparison indicate that the efficacy of panobinostat triplet therapy is similar to that of LEN/DEX in terms of PFS and OS

The median PFS and OS estimates were divided to obtain the HRs. This approach implicitly assumes exponential survival models for PFS and OS. No uncertainty around the HRs could be estimated because uncertainty was not reported for the median PFS and OS estimates for LEN/DEX. Table 25 summarises the data used in the analysis and the resulting HRs. The HRs indicate that in terms of both PFS and OS, the efficacy of PANO/BTZ/DEX was similar to that of LEN/DEX.

Table 25 Summary of data used in the indirect treatment comparison and the resulting hazard ratios (naïve comparison method) based on the a) full population and b) on the subpopulation with 2 to 3 prior lines of treatment

a)

	PANO/BTZ/DEX	**LEN/DEX**	**Hazard ratio (LEN/DEX versus PANO/BTZ/DEX)**
PFS, months	12.0	11.1	1.081
OS, months	38.24	38.0	1.006

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; OS, overall survival; PANO, panobinostat; PFS, progression-free survival.

Dimopoulos et al.,2009;[112] FDA 2014[25]

b)

	PANO/BTZ/DEX	**LEN/DEX**	**Hazard ratio (LEN/DEX versus PAN/BTZ/DEX)**
PFS, months	11.3	9.5	1.19
OS, months	[redacted]	35.8	0.959

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; OS, overall survival; PANO, panobinostat; PFS, progression-free survival.

Stadtmauer et al 2009[155]; FDA 2014[25]

Unadjusted Cox regression based comparison PANO/BTZ/DEX versus LEN/DEX

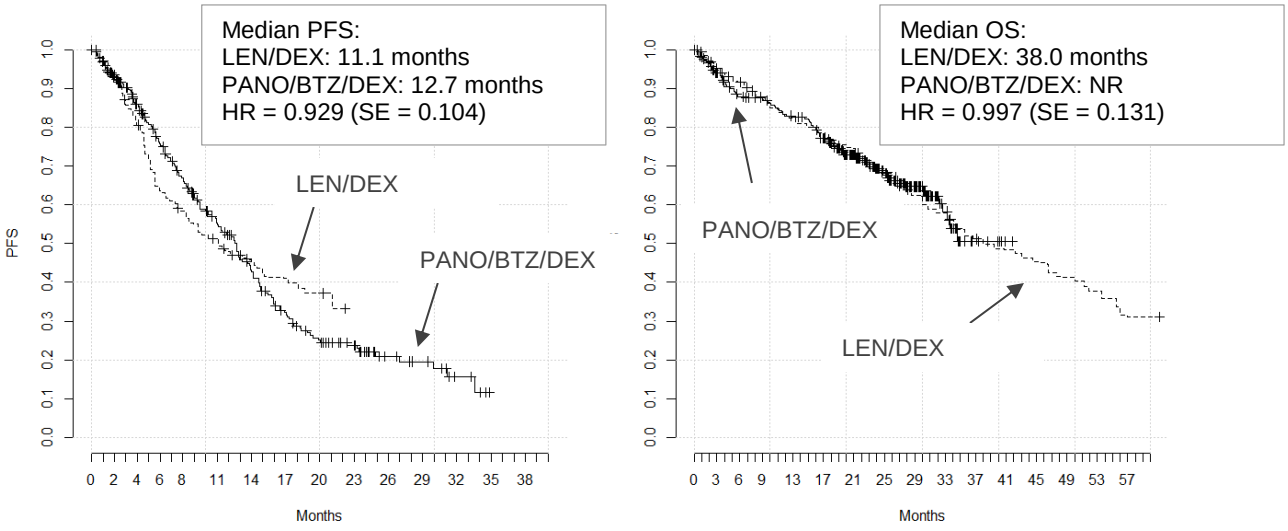
Unadjusted Cox proportion hazards regression models were set up to estimate the HR of PFS and OS between LEN/DEX against PANO/BTZ/DEX. For that, individual patient level data was simulated for LEN/DEX, whereas patient level data from the PANORAMA-1 trial, excluding patients who received prior lenalidomide treatment, was used for PANO/BTZ/DEX.

Table 26 Hazard ratios and Kaplan–Meier curves for LEN/DEX versus PANO/BTZ/DEX from the unadjusted Cox regression based comparison based on a) the full population[1] and b) on the subpopulation with 2 to 3 prior lines of treatment[2]

a)

Efficacy outcome	Hazard ratio (LEN/DEX versus PANO/BTZ/DEX)
Progression-free survival	1.062
Overall survival	1.020

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat.



N = 353 for LEN/DEX, N = 314 for PANO/BTZ/DEX

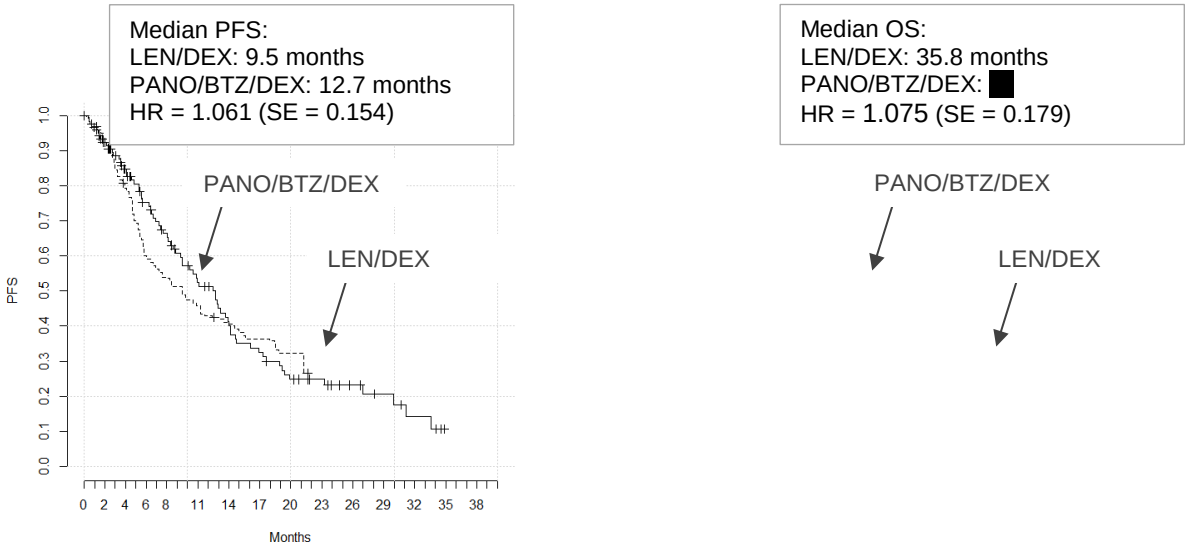
BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; NR, not reached; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; SE, standard error of the log hazard ratio.

[1] [1] Excluding patients with prior use of lenalidomide based treatment from the PANORAMA-1 dataset

[2] [2] Excluding patients with prior use of lenalidomide based treatment from the PANORAMA-1 dataset

b)

Efficacy outcome	Hazard ratio (LEN/DEX versus PAN/BTZ/DEX)
Progression-free survival	1.061
Overall survival	1.075



N = 220 for LEN/DEX, N = 142 for PANO/BTZ/DEX

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; NR, not reached; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; SE, standard error of the log hazard ratio

Matching adjusted indirect treatment comparison of PANO/BTZ/DEX versus LEN/DEX

As for the naïve comparison, the MAIC was performed for PFS and OS outcomes. This methodology has been developed to allow estimation of the relative efficacy of treatments in situations where no common comparators can be established and/or where adjustments for differences in patient populations are required. This approach is being used increasingly and has recently been applied in a number of oncology settings.[118-120]

The analysis required patient-level data for PANO/BTZ/DEX and LEN/DEX. Individual patient-level PFS and OS data together with baseline patient characteristics for the PANO/BTZ/DEX arm of PANORAMA-1 trial were used for PANO/BTZ/DEX. Data for LEN/DEX were taken from the pooled analysis of the MM-009 and MM-010 studies as reported in Dimopoulos et al 2009 as well as from the subpopulation analysis presented by Stadtmauer et al 2009.[93,155] Specifically, aggregated level data (number of patients at risk), the Kaplan–Meier curves of PFS and OS together with the baseline patient characteristics for patients receiving LEN/DEX were used. The Kaplan–Meier curves of PFS and OS together with the number of patients at risk were used to simulate individual patient-level data for LEN/DEX. (XY extract graph digitizer software was used to read in the coordinates of the published Kaplan–Meier curves

for PFS and OS. Using the coordinates of the PFS and OS curves together with the number of patients at risk, individual time to event data was generated based on the algorithm proposed by Guyot et al[121] which maps digitized Kaplan–Meier curves back to patient level data by using an iterative numerical method.)

To adjust for differences between the trials in terms of patient and disease characteristics at baseline, the matching algorithm proposed by Signorovitch et al.[122] was used. In particular, individual patient level data from the PANORMA-1 trial were reweighted such that the average/median baseline characteristics matched those reported from the MM-009/MM-010 trials. The matching ensures that treatment outcomes are comparable across balanced trial populations to the extent of the considered baseline characteristics. Ideally, matching should be based on clinically relevant risk factors that impact on the relative treatment effects. However, there is no well-established procedure regarding how the risk factors to be matched should be identified; therefore all available variables were used in this analysis. These included age, sex, time since diagnosis, ECOG score, prior number of treatments, prior treatments (IMiD and bortezomib) and serum ß2-microglobulin level.

Baseline patient characteristics before and after the adjustment of the PANORAMA-1 trial are presented in Table 27a and Table 27b. After adjustment, the patient characteristics in the two trials were virtually identical. The effective sample size (computed as the square of the summed weights divided by the sum of the squared weights) in the PANORAMA-1 trial decreased from 314 to 137 (44%) for the PANO/BTZ/DEX arm (full population[3] analysis) and from 142 to 23 (16%) (prior 2 to 3 lines of treatment analysis).

Table 27 Baseline patient characteristics used in the MAIC, before and after adjustment a) full patient population[4] and b) subpopulations with 2 to 3 prior lines of treatment

a)

Baseline characteristics, proportion of patients	**LEN/DEX (n = 353)**	**PANO/BTZ/DEX Unadjusted (n = 314)[a]**	**PANO/BTZ/DEX Adjusted (n = 137)**
Patients with median age > 63 years	50.0%	53.5%	50.0%
Male	59.5%	53.2%	59.5%
Patients with median time since diagnosis > 38.4 months	50.0%	52.5%	50.0%
ECOG 0	43.1%	42.7%	43.1%

[3] Excluding patients with prior use of lenalidomide based treatment from the PANORAMA-1 dataset

[4] Excluding patients with prior use of lenalidomide based treatment from the PANORAMA-1 dataset

Patients receiving ≥ 2 prior therapies	64.9%	48.7%	64.9%
Previous THAL	36.0%	55.1%	36.0%
Prior BTZ	7.6%	43.0%	7.6%
Prior SCT	58.4%	55.1%	58.4%
Serum ß2-microglobulin (> 2.5 mg/L)	70.8%	71.0%	70.8%

[a]The MM-009/MM-010 trials excluded patients who had previously received LEN. Therefore, to match the patient selection criteria, PANO/BTZ/DEX patients who had received prior LEN/DEX were excluded from the analysis set (n = 315). A further patients was excluded due to lack of complete information on all covariates (n = 314) .

BTZ, bortezomib; DEX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; LEN, lenalidomide; PANO, panobinostat; SCT, stem cell transplant; THAL, thalidomide.

b)

Baseline characteristics, proportion of patients	**LEN/DEX (n = xxx)**	**PANO/BTZ/DEX Unadjusted[a] (n = 142)**	**PANO/BTZ/DEX Adjusted (n = 23)**
Patients with median age > 63 years	50%	48.6%	50%
Male	58.2%	53.5%	58.2%
Patients with median time since diagnosis > 49.2 months	50%	47.2%	50%
ECOG 0 to 1	85.5%	38.0%	85.5%
Previous THAL	51.8%	63.4%	11.4%
Prior BTZ	11.4%	59.2%	53.2%
Prior SCT	53.2%	56.3%	74.5%
Serum ß2-microglobulin (> 2.5 mg/L)	74.5%	67.6%	50%

[a] The MM-009/MM-010 trials excluded patients who had previously received LEN. Therefore, to match the patient selection criteria, PANO/BTZ/DEX patients who had received prior LEN/DEX were excluded from the analysis set (n = 188). For the prior 2-3 LoT analysis, all patients had complete information on the covariates.

BTZ, bortezomib; DEX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; LEN, lenalidomide; PANO, panobinostat; SCT, stem cell transplant; THAL, thalidomide.

Stadtmauer et al, 2009[155]

Results of the matching adjusted indirect treatment comparison indicate that the efficacy of panobinostat triplet therapy is similar to that of LEN/DEX in terms of PFS and OS

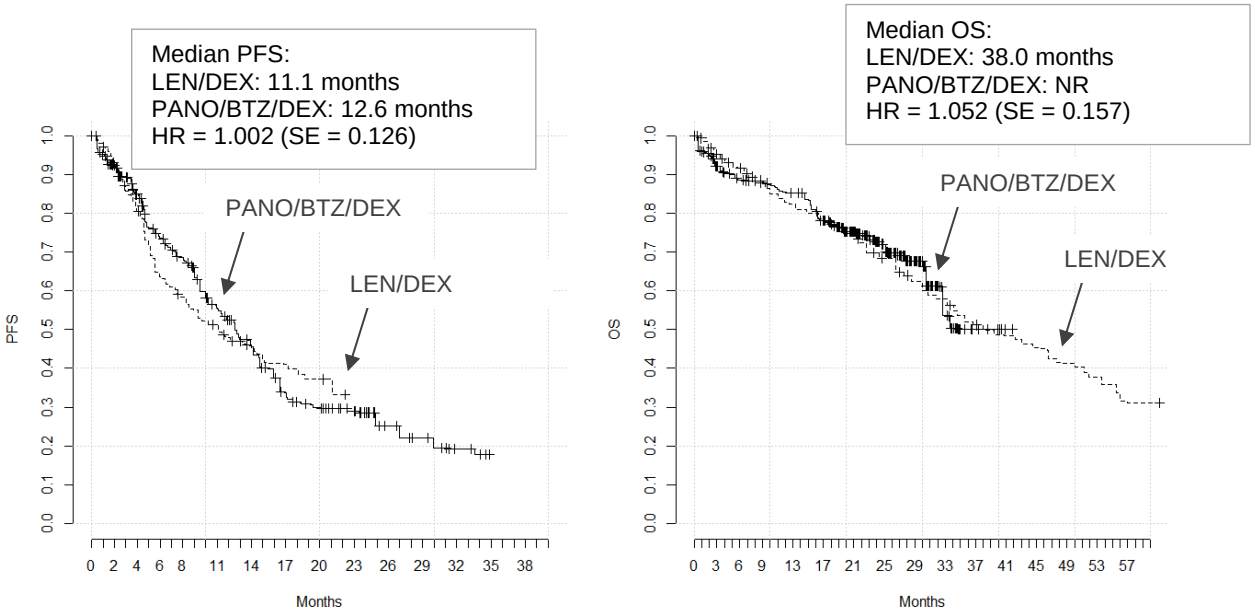
Results of the MAIC indicated that in terms of both PFS and OS, the efficacy of PANO/BTZ/DEX was similar to that of LEN/DEX (Table 28).

Table 28 Hazard ratios and Kaplan–Meier curves for LEN/DEX versus PANO/BTZ/DEX from the MAIC based on the a) full population[5] and b) on the subpopulation with 2 to 3 prior lines of treatment[6]

a)

Efficacy outcome	Hazard ratio (LEN/DEX versus PANO/BTZ/DEX)
Progression-free survival	1.002
Overall survival	1.052

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PANO, panobinostat.



N = 353 for LEN/DEX, N = 137 for PANO/BTZ/DEX

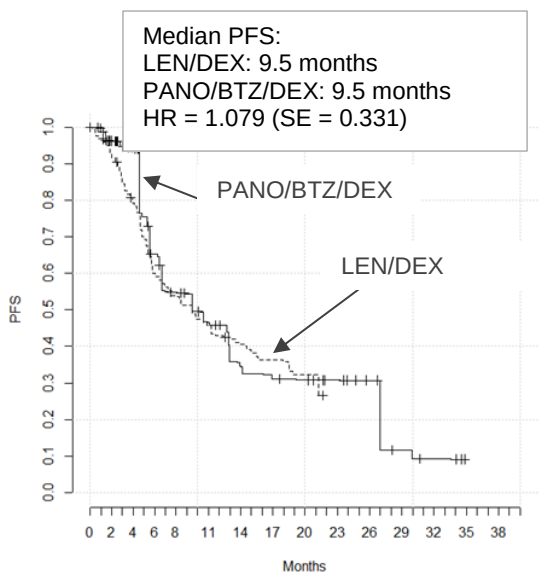
BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; NR, not reached; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; SE, standard error of the log hazard ratio

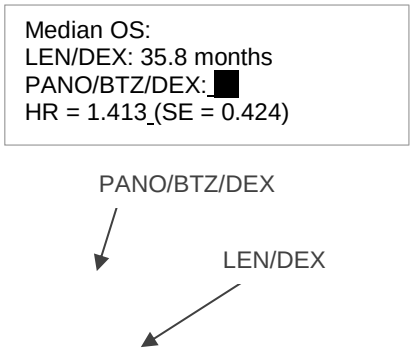
b)

Efficacy outcome	Hazard ratio (LEN/DEX versus PANO/BTZ/DEX)
Progression-free survival	1.108
Overall survival	1.413

[5] Excluding patients with prior use of LEN based treatment from the PANORAMA-1 trial

[6] Excluding patients with prior use of LEN based treatment from the PANORAMA-1 trial





N = 220 for LEN/DEX, N = 22.5 for PANO/BTZ/DEX (one patient discarded after matching because of the extreme weight estimated for that patient)
BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; NR, not reached; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; SE, standard error of the log hazard ratio

Table 29 summarises the HRs for LEN/DEX versus PANO/BTZ/DEX obtained by the four different indirect treatment comparison methods. As summarised in Table 22 and discussed in section 4.10.5 each methods has a number of advantages and disadvantages. For the analysis presented here we suggest that the MAIC provides the most appropriate approach for deriving the relative efficacies of the PANO/BTZ/DEX versus LEN/DEX for use in the economic evaluation.

Table 29 Summary of the hazard ratios for LEN/DEX versus PANO/BTZ/DEX obtained by the four/three different indirect treatment comparison methods based on the a) full population and b) on subpopulations with 2 to 3 prior lines of treatment

a)

	Common comparators method	Naive comparison	Unadjusted Cox	Matching adjusted indirect treatment comparison
Progression-free survival	1.870	1.081	0.929	1.062
Overall survival	1.216	1.006	0.997	1.020

b)

	Naive comparison	Unadjusted Cox	Matching adjusted indirect treatment comparison
Progression-free survival	1.190	1.061	1.108
Overall survival	0.959	1.075	1.413

BTZ, bortezomib; DEX, dexamethasone; lenalidomide; PANO, panobinostat;

For all comparisons considered in the three approaches described here, no situation occurred where both indirect and direct evidence was available. Therefore it was not possible to assess possible inconsistencies between the direct and indirect evidence available.

4.10.5 Risk of bias

Common comparator method

Results of the common comparator method could be biased for the following reasons:

1. This methodology implicitly assumes that covariates acting as potential relative treatment-effect modifiers (eg, prior bortezomib) are balanced across trials or any heterogeneity in these risk factors does not impact the analysis results.
2. For PFS, TTP and OS, the analysis was based on using HRs and relied on the assumption that the relative risk between the two treatment groups remained the same throughout the follow-up period, which may not be true in these trials.

Naïve comparison of PANO/BTZ/DEX versus LEN/DEX

This analysis did not adjust for differences in trial design and patient populations. It implicitly assumed that differences in trial design and patient populations do not influence the relative efficacy outcomes (ie, hazard ratio of PFS and OS). Furthermore, it implicitly assumed that the risk of experiencing a PFS or OS event follows an exponential distribution which may not be true.

Matching adjusted indirect comparison

There are a few inherent limitations in this methodological approach that add uncertainty to the reported results. First, the matching algorithm could only adjust for differences in baseline characteristics that were reported in both PANORMA-1 and the MM-009/010 trials. Although the analyses adjusted for several characteristics, there may be some remaining differences between the patient populations that could bias the treatment comparison. In particular, the use of a different mix of subsequent antineoplastic therapies may affect the OS comparison; however this bias often applies when comparing treatments arms with a randomised controlled trial in rrMM since treatments after the randomised treatment are not specified in the study protocol. As patient-level data were not available for the MM-009/010 trials patient-

level data had to be simulated. Although the simulated data replicated the observed data very well, this procedure introduces uncertainty.

4.10.6 Cost-effectiveness analysis

For the cost-effectiveness analysis of panobinostat triplet therapy compared with LEN/DEX in the third-line setting or later, the HRs for PFS and OS for this comparison (see Table 29) were applied to two of the possible subgroups described in section 4.8. These subgroups are defined to be in line with NICE TA171[87] and the current clinical practice in England and Wales.[60]

4.11 Non-randomised and non-controlled evidence

4.11.1 Overview

Two published non-RCTs provide supporting evidence for the efficacy and safety of panobinostat in combination with BTZ/DEX relative to BTZ/DEX alone. These are a phase 2 trial, PANORAMA-2,[10] and an earlier dose-escalation/safety phase 1b trial (Table 30).[11]

Table 30 List of relevant non-randomised controlled trials of panobinostat in relapsed/refractory multiple myeloma

Trial number (acronym)	Intervention	Population	Objectives	Primary study reference	Justification for inclusion
DUS71 PANORAMA-2 NCT01083602 Phase 2 multi-centre single-arm open-label study	PANO/BTZ/DEX	Patients with relapsed and BTZ-refractory MM N = 55	To compare the efficacy and safety of PANO/BTZ/DEX versus BTZ/DEX for treatment of rrMM *Primary endpoint*: ORR *Secondary endpoints:* MR, TTR, DoR, PFS, TTP, OS, safety and tolerability	Richardson *et al. Blood* 2013;122:2331–7[10]	Provides efficacy and safety data for PANO/BTZ/DEX
B2207 Phase 1b study NCT00532389 Phase 1b multicentre open-label post dose-escalation study	PANO/BTZ/DEX	Patients with relapsed rrMM N = 62 (15 in dose expansion phase)	To determine the maximum tolerated dose of PANO in combination with BTZ/DEX and to evaluate safety, pharmacodynamics/pharmacokinetics, and efficacy *Primary endpoint:* Confirmation of MTD *Secondary endpoints:* Safety and tolerability, PK and PD of biomarkers, preliminary efficacy	San-Miguel et al. *J Clin Oncol* 2013;31:3696−703[11]	Provides efficacy and safety data for PANO/BTZ/DEX

BTZ, bortezomib; DEX, dexamethasone; DoR, duration of response; MM, multiple myeloma; MR, minimal response; MTD, maximum-tolerated dose; ORR, overall response rate; OS, overall survival; PANO, panobinostat; PD, pharmacodynamic; PFS, progression-free survival; PK, pharmacokinetics; rrMM, relapsed/refractory multiple myeloma; TTP, time to progression; TTR, time to response.

4.11.2 The PANORAMA-2 study

The results from the PANORAMA-2 trial, a phase 2, single-arm, open-label, multicentre study that investigated the efficacy and safety of PANO/BTZ/DEX in patients with relapsed MM who

were refractory to bortezomib,[10] suggest that panobinostat can restore sensitivity to bortezomib and improve median PFS and OS in responsive patients.

Patient selection

The key patient selection criteria were similar between the phase 2 and phase 3 trials, as summarised in Table 31, with the exception that patients refractory to bortezomib were excluded from PANORAMA-1 but were eligible for entry to PANORAMA-2.

Table 31 Comparison of key inclusion and exclusion criteria for the PANORAMA-1 and PANORAMA-2 studies

	PANORAMA-1	PANORAMA-2
Inclusion criteria		
Age > 18 years	✓	✓
Measurable relapsed or relapsed and refractory MM with 1 to 3 previous treatments	✓	–
Measurable relapsed and BTZ- refractory MM with ≥ 2 previous treatments and exposed to an IMiD	–	✓
Eastern Cooperative Oncology Group performance status of ≤ 2	✓	✓
ANC	≥ 1.5 × 10^9 cells/L	≥ 1.0 × 10^9 cells/L
Platelet count	≥ 100 × 10^9 cells/L	≥ 70 × 10^9 cells/L
Adequate liver function	✓	✓
Peripheral neuropathy < grade 2	✓	✓
Exclusion criteria		
Primary refractory MM	✓	✓
BTZ-refractory MM	✓	–

ANC, absolute neutrophil count; BTZ, bortezomib; IMiD, immunomodulatory drug; MM, multiple myeloma;

Methods

The study involved 55 heavily pre-treated bortezomib-refractory adult patients who had received at least two prior lines of therapy (median of four lines) including IMiDs; all patients had previously received bortezomib and 98% had received prior lenalidomide. All patients received PANO/BTZ/DEX administered as in the PANORAMA-1 study (ie, a 3-week repeating cycle consisting of 2 weeks on treatment and 1 week off treatment, in two treatment phases: in treatment phase 1 [cycles 1 to 8], panobinostat [20 mg] was administered three times a week, bortezomib [1.3 mg/m^2] was administered twice a week and dexamethasone [20 mg] was administered four times a week, whereas in treatment phase 2 [cycles 9 +], panobinostat

and dexamethasone were administered as for treatment phase 1 and bortezomib was given once a week). The primary study endpoint was ORR, whilst secondary endpoints were MR, time to response, duration of response, PFS, OS, and safety and tolerability of the triplet therapy. Response to therapy was assessed based on modified EBMT (mEBMT) criteria after 8 cycles of therapy.

Efficacy

Table 32 summarises the tumour responses achieved. A third of patients achieved a PR or better (ORR: n = 19; 34.5%) including one patient who experienced nCR (1.8%), although no patients experienced a CR. A higher ORR was observed in patients who did not receive bortezomib in their last line of therapy (n = 28; 42.9%) versus those who did (n = 27; 25.9%). Furthermore, because 18.2% of patients overall achieved MR (n = 10), the clinical benefit rate (≥ MR) was 52.7% (n = 29).

Median PFS was 5.4 months overall, and was longer in patients who progressed within 60 days of being off their previous bortezomib-containing regimen (7.6 months) than in those who progressed while receiving bortezomib (4.2 months). In patients who experienced a PR or better, the median time to response was 1.4 months and the median duration of response was 6 months.

At a median follow-up of 8.3 months, median OS was not yet reached in the original publication. However, updated data presented in abstract form, reported a median OS of 17.5 months (95% CI, 10.8 to 25.2 months).[24] In a *post hoc* analysis, the 19 patients who achieved a greater than PR had a median PFS of 7.6 months (95% CI, 5.8 to 9.7 months) and a median OS of 25.2 months (95% CI, 17.5 to 25.2 months), while the 36 patients with a greater than PR had a median PFS of 2.6 months (95% CI, 2.1 to 4.9 months) and a median OS of 9.9 months (95% CI, 5.4 to 17.4 months).

Table 32 Tumour responses reported in the PANORAMA-2 study at the end of eight cycles

Best response at the end of eight cycles (confirmed at 6 weeks)	**Number of patients, n (%) n = 55**
Overall response	19 (34.5)
Complete response	0 (0.0)
Near-complete response	1 (1.8)
Partial response	18 (32.7)
Minimal response (MR)	10 (18.2)
Clinical benefit rate (≥ MR)	29 (52.7)
Stable disease	20 (36.4)
Progressive disease	3 (5.5)
Unknown[a]	3 (5.5)

[a]Patients without post-baseline assessments.

MR, minimal response.

Richardson et al. 2013[10]

Safety

At the time of data cut-off, a total of 87.3% of patients had discontinued treatment as a result of disease progression (56.4%, n = 31), adverse events (18.2%, n = 10), withdrawal of consent (9.1%, n = 5), death (1.8%, n = 1) or the start of a new cancer therapy (1.8%, n = 1). Furthermore, dose reductions were required in 63.6%, 65.5% and 27.3% of patients for panobinostat, bortezomib and dexamethasone, respectively, and median relative dose intensities were 72.9%, 79.8% and 87.5%, respectively. Treatment interruptions of panobinostat, bortezomib, and dexamethasone occurred in 32 (58.2%), 27 (49.1%), and 40 (72.7%) patients, respectively..

Non-haematological and haematological adverse events were predictable and manageable. Diarrhoea (20.0%), fatigue (20.0%) and pneumonia (14.5%) were the only grade 3 to 4 non-haematological toxicities reported in 10% or more of patients. Furthermore, 9.1% of patients experienced grade 3/4 asthenia (Table 33). Asthenia/fatigue was managed with hydration, dose reduction and supportive care. The most frequently reported grade 3 to 4 haematological events were thrombocytopenia (63.6%), neutropenia (14.6%) and anaemia (14.5%). No patients discontinued owing to thrombocytopenia, which was managed by dose reduction in 23 patients (41.8%) and platelet transfusions (median of two) in 24 patients (43.6%).

One patient died during the study and three patients died within a month of discontinuing study treatment. None of the deaths were considered related to study treatment.

Table 33 Haematological and non-haematological adverse events regardless of study drug relationship occurring in the PANORAMA-2 study.

Adverse events, %	**PANO/BTZ/DEX (n = 55)**
Non-haematological adverse events reported in > 5% of patients in treatment group: any grade/grade 3 or 4 (% patients)	
Diarrhoea	71/20
Fatigue	69/20
Nausea	60/6
Hypokalaemia	22/7
Hypotension	20/9
Asthenia	20/9
Abdominal distention	20/7
Pneumonia	16/15

Dehydration	16/5
Abdominal pain	16/6
Flatulence	11/6
Sepsis	9/9
Syncope	9/9
Septic shock	6/6
Hypophosphatemia	6/6
Haematological adverse events reported in > 5% of patients in treatment group: any grade/grade 3 or 4 (% patients)	
Thrombocytopenia	66/64
Anaemia	47/15
Neutropenia	18/15

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

Richardson et al. 2013[10]

4.11.3 Phase 1b trial

A single-arm, open-label, phase 1b study (NCT00532389) evaluated PANO/BTZ/DEX in patients with rrMM, including a subset of patients refractory to bortezomib therapy.[11] The study aimed to determine the maximum tolerated dose of panobinostat and bortezomib, and to evaluate safety, pharmacodynamics/pharmacokinetics, and efficacy.

The phase 1b dose-finding Study (B2207) was initiated for the combination of panobinostat with bortezomib in patients with relapsed or relapsed and refractory MM, following at least one prior line of therapy. This study determined a maximum tolerated dose of 20 mg panobinostat dosed three times a week in combination with bortezomib 1.3 mg/m^2. Doses of 10 mg to 30 mg panobinostat (three times a week, until progression) in combination with 1.0 mg/m^2 or 1.3 mg/m^2 bortezomib administered intravenously (on days 1, 4, 8 and 11 of a 21-days cycle) were tested. The maximum tolerated dose was defined as the highest dose level of panobinostat in combination with bortezomib in the specified dosing schedule that met the overdose control criteria based on dose limiting toxicities observed in cycle 1 and additional safety information.

Dose limiting toxicities were reported in three of 15 patients (20%) in the maximum tolerated dose cohort. Thrombocytopenia as a dose limiting toxicity (Dose limiting toxicities ≥ grade 3) was reported by one of 15 patient (6.7%) in the maximum tolerated dose cohort compared to more than 15% in the cohorts with higher doses of panobinostat. Of note, four patients in the maximum tolerated dose cohort (23.5%) received more than 12 months of therapy. In the dose-escalation phase of the study, overall response rates were highest in the cohorts using a dose of bortezomib of 1.3 mg/m^2 and a dose of panobinostat ≥ 20 mg, ranging from 52.9% to 57.1%.

Subsequently, on the basis of a pooled analysis and a pharmacokinetic- pharmacodynamic modelling of single-agent panobinostat-induced thrombocytopenia suggesting that drug holidays should be effective to allow recovery of platelet counts, a dosing schedule of 2 weeks on and 1 week off therapy at panobinostat dose of 20 mg was introduced into the dose expansion phase of the phase 1 study and in PANORAMA-1 to manage thrombocytopenia and to allow for accelerated platelet recovery .The backbone regimen of intravenous bortezomib at a dose of 1.3 mg/m^2 administered on days 1, 4, 8, 15 of 21-days treatment cycles was the standard approved regimen used in 2009 when the phase 3 and phase 2 studies were initiated.

Methods

In the dose-escalation phase, panobinostat was given orally at a dose of 10 mg to 30 mg three times weekly, with bortezomib administered intravenously at a dose of 1.0 mg/m^2 or 1.3 mg/m^2 on days 1, 4, 8 and 11 during a 21-day treatment cycle. Dexamethasone was to be added in case of suboptimal response from cycle 2 onwards. A modified treatment schedule for panobinostat (2 weeks on, 1 week off) was evaluated in a dose-expansion phase of the study and dexamethasone was introduced for all patients from cycle 2 onwards. A total of 62 patients were enrolled (dose-escalation phase 47 patients; dose-expansion phase 15 patients).

Maximum tolerated dose and efficacy

Based on 15 evaluable patients, the maximum tolerated dose was declared at 20 mg panobinostat three times a week and 1.3 mg/m^2 bortezomib. Dose limiting toxicities were reported in 3/15 patients (20%) in the maximum tolerated dose cohort. Thrombocytopenia as a dose limiting toxicity (dose limiting toxicity ≥ grade 3) was reported by 1/15 patient (6.7%) in the maximum tolerated dose cohort compared to more than 15% in the cohorts with higher doses of panobinostat. Of note, 4 patients in the maximum tolerated dose cohort (23.5%) received more than 12 months of therapy. Objective responses were achieved in 21 of 47 patients (45%) in the dose-escalation phase of the study and 11 of 15 evaluable patients (73%) in the dose-expansion part of the study. In addition, 4 patients achieved a MR in the dose-escalation phase. Among patients refractory to bortezomib (n = 19), the ORR was 26% and 42% achieved at least a MR.

Safety

Common grade 3/4 adverse events (incidence ≥ 15%) reported from this study included thrombocytopenia (81%), neutropenia (60%), asthenia (26%), anaemia (18%), leukopenia (18%) and diarrhoea (16%). Further analysis of these data has linked the incidence of grade 3/4 diarrhoea to the dose escalation of bortezomib from 1.0 mg/m^2 to 1.3 mg/m^2.

4.12 Adverse reactions

No trials were identified that were designed to primarily assess safety. Safety data are reported for the phase 1b and phase 2 studies (see section 4.11) and for the phase 3 PANORAMA-1 study (described below).

4.12.1 Drug exposure

Safety data have been reported for the PANORAMA-1 trial that included 381 patients randomised to receive PANO/BTZ/DEX and 377 patients randomised to placebo/BTZ/DEX. Patients were followed for a median of 31 months. Patients received treatment for a median of 5.0 months (IQR 2.23 to 10.75) in the panobinostat group and 6.1 months (IQR 2.82 to 10.75) in the control group; the corresponding mean ± SD values are 6.0 ± 4.13 months (panobinostat) and 6.4 ± 3.89 months (control group).[9,25] The numbers of patients in the safety set who required at least one dose change in the panobinostat group were 194 (51%) for panobinostat, 231 (61%) for bortezomib and 93 (24%) for dexamethasone; in the placebo group the equivalent numbers were 86 (23%) for placebo, 158 (42%) for bortezomib and 65 (17%) for dexamethasone. The median relative dose intensities for the panobinostat group were 80.7%, 75.7% and 87.5% for panobinostat, bortezomib and dexamethasone, respectively. In the control group the corresponding values were 95.1%, 86.7% and 95.1% for placebo, bortezomib and dexamethasone, respectively, suggesting that receiving a higher dose intensity for bortezomib and dexamethasone does not provide the efficacy advantage achieved with the addition of panobinostat.

4.12.2 Safety profile

Table 34 summarises the safety data from the PANORAMA-1 study.

Table 34 Adverse events across randomised groups in the PANORAMA-1 study.

Adverse event	**PANO/BTZ/DEX (n = 381)**	**PBO/BTZ/DEX (n = 377)**
Death[a] n (%)	30 (8)	18 (5)
SAEs, n (%)	228 (60)	157 (42)
Grade 3 or 4 adverse events, n (%)	364 (96)	310 (82)
Withdrawal due to adverse events, n (%)	138 (36)	77 (20)
Non-haematological adverse events reported in > 10% of patients in either treatment group: any grade/grade 3 or 4, (% of patients).		
Diarrhoea	68/25	42/8
Peripheral neuropathy	61/18	67/15
Asthenia or fatigue	57/24	41/12

Adverse event	PANO/BTZ/DEX (n = 381)	PBO/BTZ/DEX (n = 377)
Nausea	36/6	21/1
Peripheral oedema	29/2	19/1
Decreased appetite	28/3	12/1
Constipation	27/1	33/2
Pyrexia	26/1	15/2
Vomiting	26/7	13/1
Cough	21/1	19/0
Insomnia	19/0	16/1
Dizziness	19/3	16/2
Upper respiratory tract infection	18/2	15/2
Pneumonia	17/13	13/10
Dyspnoea	15/2	12/2
Hypotension	14/3	9/2
Headache	14/1	11/1
Abdominal pain	13/2	11/1
Nasopharyngitis	13/0	12/1
Back pain	13/1	12/1
Dyspepsia	12/1	11/0
Upper abdominal pain	12/1	10/1
Weight decreased	12/2	5/0
Pain in extremity	10/1	14/1
Herpes zoster	5/1	11/2
Haematological adverse events reported in > 10% of patients in either treatment group: any grade/grade 3 or 4, (% of patients)		
Thrombocytopenia	98/67	84/31
Neutropenia	75/34	36/11
Anaemia	62/18	52/19
Adverse events leading to discontinuation in ≥1% of patients in either treatment group (% of patients)		
Fatigue	2.9	2.9
Diarrhoea	4.5	1.6
Asthenia	2.9	0
Pneumonia	1.3	2.1
Peripheral neuropathy	3.7	1.9
Thrombocytopenia	1.6	0.5
Infection	5.0	3.7

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; PBO, placebo; SAE, serious adverse event.

[a]Deaths occurring more than 28 days after the discontinuation of study treatment are not summarised San-Miguel et al.,2014;[9] FDA 2014[25]

In the PANORAMA-1 study, most patients in both groups experienced grade 3/4 adverse events (PANO/BTZ/DEX 96%, n = 364; BTZ/DEX 82%, n = 310) (Table 34). A proportion of

patients in both the panobinostat (36%, n = 138) and control (20%, n = 77) groups discontinued owing to adverse events, and non-fatal serious adverse events occurred in 60% of patients in the panobinostat group (n = 228) and 42% in the control group (n = 157). The most frequent (≥ 2%) adverse events leading to treatment discontinuation were diarrhoea, fatigue, asthenia and peripheral neuropathy in the panobinostat group and fatigue and pneumonia in the control group (Table 34).

The incidence of adverse events was much lower during cycles 9 to 12 (treatment phase 2) when bortezomib and dexamethasone were administered less frequently

An analysis of the incidence of adverse events in patients who completed cycles 9 to12 of the study showed that the incidence of newly occurring or worsening grade 3/4 adverse events was much lower during cycles 9 to 12 compared with the first 8 cycles (Table 35).[97] Thus the only grade 3/4 adverse events occurring in 5% or more of patients in the panobinostat group in cycles 9 to 12 were diarrhoea (7.1% versus 24.1% in phase1 and 2) and thrombocytopenia (6% versus 56.7% in phase 1 and 2). Furthermore, the overall rate of AEs decreased in treatment phase 2 (cycles 9 to 12) when both bortezomib and dexamethasone were administered less frequently compared with treatment phase 1. The median dose intensity of panobinostat was also reduced, by approximately 25% by cycle 4; this reduced median dose intensity was then maintained for cycles 5 to 12 (Figure 31). Together, these data support optimizing the management of adverse events for patients who receive PANO/BTZ/DEX through dose adjustments or interruptions and/or supportive therapy. These data also support once-weekly administration of bortezomib when used in combination with panobinostat and dexamethasone.

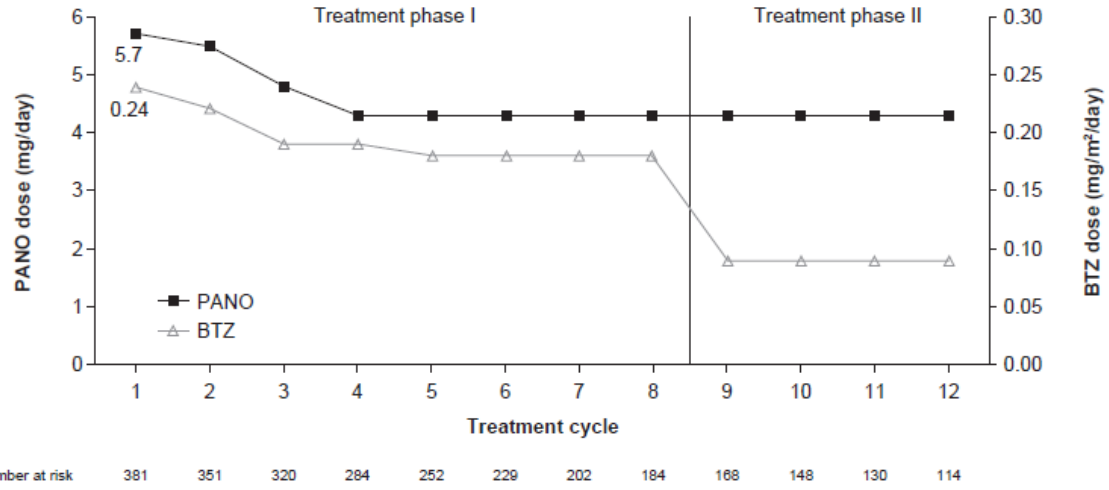
Table 35 Adverse events occurring in >30% of patients in either treatment group according to treatment phase in the PANORAMA-1 study

	Treatment phase 1		**Treatment phase 2**	
AE any grade/grade 3/4, %	**PANO/BTZ/DEX (n = 381)**	**PBO/BTZ/DEX (n = 377)**	**PANO/BTZ/DEX (n = 168)[a]**	**PBO/BTZ/DEX (n = 193)[a]**
Diarrhoea	65.9/24.1	38.2/8.0	29.8/7.1	20.2/0
Thrombocytopenia	64.3/56.7	40.1/24.4	18.5/6.0	5.2/1.0
Anaemia	39.9/15.5	31.8/15.1	13.7/3.0	9.3/3.6
Fatigue	39.6/16.3	28.9/8.8	8.9/1.8	4.7/0
Nausea	35.2/5.5	19.4/0.5	5.4/0	4.7/0
Peripheral neuropathy	29.4/6.0	32.9/4.8	6.5/3.0	11.9/1.6

Constipation	26.0/1.0	31.8/1.1	3.6/0	5.7/0

[a]One patient randomly assigned to receive panobinostat was given placebo during cycles 1 and 2 because of a allocation error; the patient was subsequently given panobinostat from cycle 3 until discontinuation of treatment but was included in the placebo group for the safety analysis.
AE, adverse event; BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; PBO, placebo
San Miguel et al 2014[97]

Figure 31 Median dose intensity of panobinostat and bortezomib in the PANO/BTZ/DEX group by treatment cycle in the PANORAMA-1 study



[a] PANO: Dose intensity of 5.7 mg/day corresponds to 20 mg 3 times per week on the 2 weeks on/1 week off schedule
[b] BTZ: Dose intensity of 0.24 mg/m2/day corresponds to 1.3 mg/m2 twice per week on same schedule
BTZ, bortezomib; PANO, panobinostat.
San Miguel et al 2014[97]

Diarrhoea, asthenia and fatigue were the most frequently reported non-haematological grade 3/4 adverse events associated with panobinostat triplet therapy

The most frequently reported non-haematological adverse events of any grade (reported in ≥ 40% of patients in either group) in both the panobinostat and control groups were diarrhoea (68% versus 42%), peripheral neuropathy (61% versus 67%) and asthenia/fatigue (57% versus 41%) (Table 34). The most common grade 3/4 events (reported in ≥ 15% of patients in either group) in the panobinostat and control groups, respectively, were diarrhoea (25% versus 8%), asthenia/fatigue (24% versus 12%) and peripheral neuropathy (18% versus 15%), and all were more common in the panobinostat group. Grade 3/4 nausea and vomiting were also reported more frequently in the panobinostat group than in the placebo group (nausea, 6% versus 1%; vomiting, 7% versus 1%, respectively).

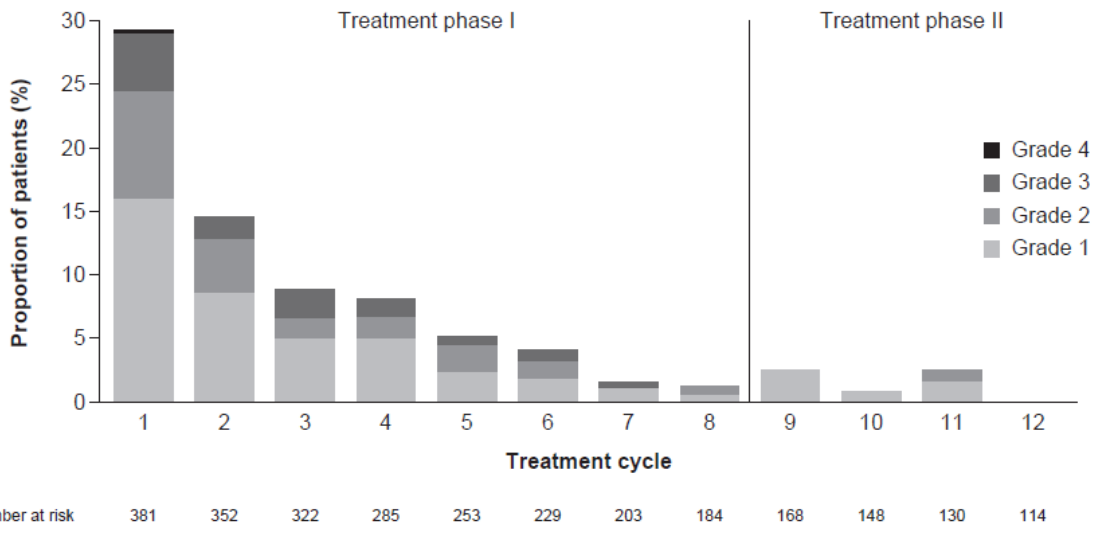
The observed safety profile, in terms of both type and frequency of adverse events, was consistent with the known safety profile of PANO/BTZ/DEX and BTZ/DEX and thus was manageable with established intervention techniques. In both the panobinostat and control groups, only a small proportion of patients discontinued owing to asthenia of fatigue of any grade (panobinostat, 6%; control, 3%).

Diarrhoea was managed by dose adjustment or interruption and anti-diarrhoeal medication in most patients

The majority of patients with diarrhoea experienced their first incidence during the first few cycles (Figure 32). The first incidence of diarrhoea was primarily grade 1/2.[97] The pattern and grade of diarrhoea in patients who received PANO/BTZ/DEX was consistent with a relatively low rate of grade 3/4 events (range, 0.5% to 8.4%) during each cycle.

Diarrhoea was managed by dose adjustment or interruption and anti-diarrhoeal medication, and few patients discontinued treatment owing to this adverse event of any grade (panobinostat, 4%; control, 2%). Studies suggest that early intervention and/or alternative dosing strategies may help to improve tolerability: both subcutaneous administration of bortezomib and administration on a weekly schedule are associated with a reduced incidence of gastrointestinal toxicities.[123] Consistent with this, in the phase 1b study severe diarrhoea was only observed in cohorts of patients who received bortezomib at a dose of 1.3 mg/m^2, and not those who received bortezomib at the lower dose of 1.0 mg/m^2, regardless of the panobinostat dose given (see section 4.11.3).

Figure 32 Rate of newly-occurring diarrhoea by cycle for patients receiving panobinostat triplet therapy in the PANORAMA-1 study



[a]Denominator for each cycle based on number of patients at risk

San Miguel et al 2014[97]

Panobinostat triplet therapy was not associated with an increased risk of grade 3/4 peripheral neuropathy versus BTZ/DEX

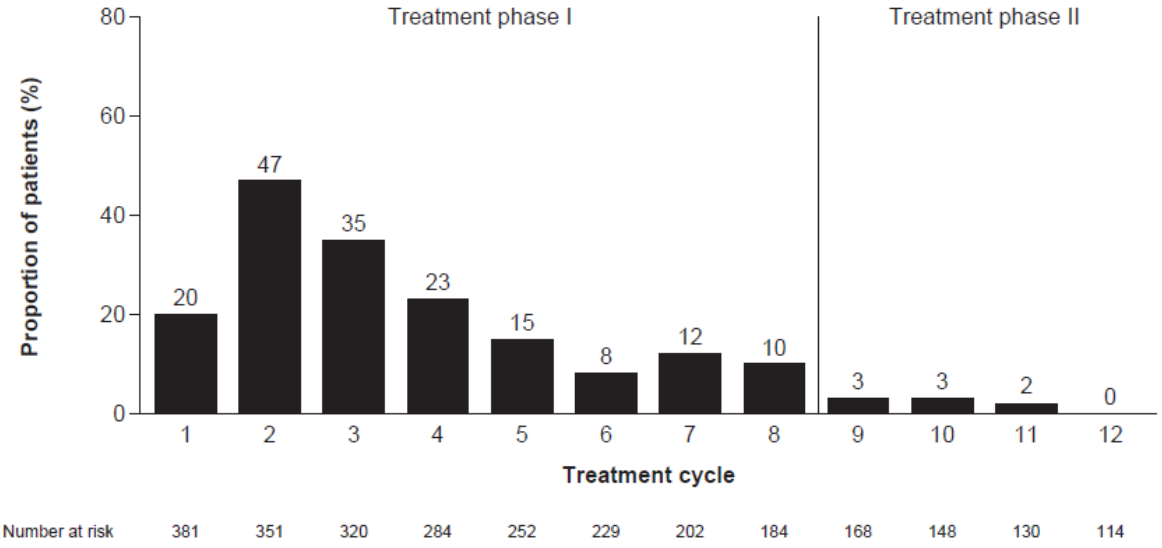
The proportion of patients experiencing peripheral neuropathy was similar in the panobinostat and control groups when considering events of any grade (61% versus 67%, respectively) or those of grade 3/4 (18% versus 15%, respectively). Grade 3/4 peripheral neuropathy led to treatment discontinuation in eight patients (2.1%) in the panobinostat group and three patients (0.8%) in the control group. Peripheral neuropathy of any grade led to treatment discontinuation in 14 patients (4%) and seven patients (2%) in the panobinostat and control groups, respectively

Thrombocytopenia was the most frequently reported grade 3/4 haematological adverse event associated with panobinostat triplet therapy, but was reversible and non-cumulative and rarely led to treatment discontinuation

Newly occurring or worsening thrombocytopenia of any grade was reported by 98% and 84% of patients in the panobinostat and control groups, respectively; the corresponding proportions for grade 3/4 thrombocytopenia were 67% and 31%, respectively. However, few patients discontinued in either group owing to thrombocytopenia of any grade (panobinostat, 2%, n = 6; control, 1%, n = 2), or grade 3/4 events (panobinostat, 1.3%, n = 5; control, 0.5%, n = 2), indicating that thrombocytopenia was effectively managed by dose adjustment, treatment interruption or platelet transfusions. Most grade 3/4 events occurred during the first four cycles of therapy and the incidence of grade 3/4 thrombocytopenia in treatment phase 2 was less than 5% for each cycle (Figure 33).

Thrombocytopenia was managed by dose adjustment or treatment interruption in 31% and 11% of patients in the panobinostat and control groups, respectively, for thrombocytopenia of any grade and in 30% and 9%, respectively, for grade 3/4 thrombocytopenia. Alternatively, thrombocytopenia was managed with platelet transfusions, with a higher proportion of patients in the panobinostat group (33%) receiving this treatment than in the control group (10%). The mean duration for which patients received platelet transfusions was 4.9 days and 6.0 days for the panobinostat and control groups, respectively. Analysis of platelet kinetics during treatment showed that median platelet counts recovered to baseline levels at the beginning of each cycle (following the treatment-free week) (Figure 34). This is consistent with the observation in earlier studies that thrombocytopenia associated with panobinostat appears to be due to defects in platelet production or release rather than loss of megakaryoctyes.[25] Few patients experienced grade 3/4 haemorrhage in either treatment group (panobinostat, 4%; control, 2%). Approximately one-fifth of patients in both treatment groups experienced grade 3/4 anaemia (panobinostat, 18%; control, 19%).

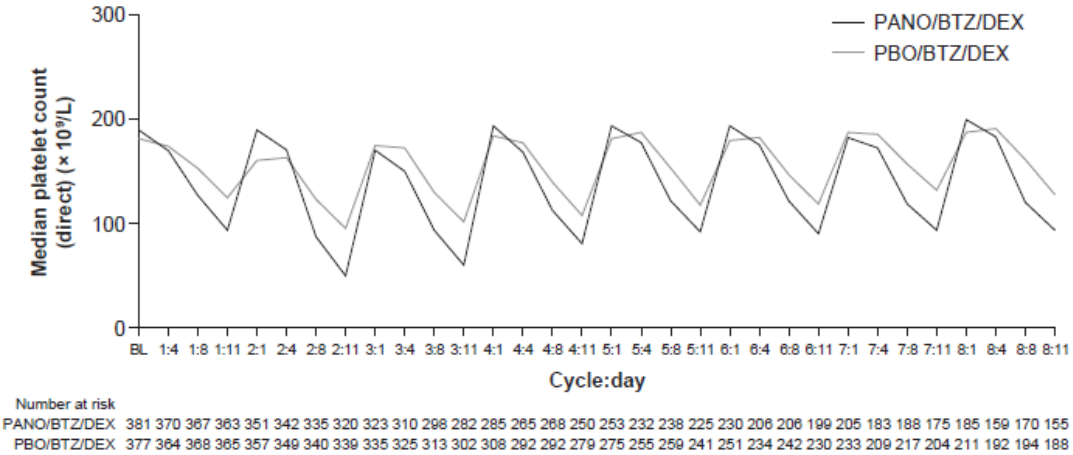
Figure 33 Rate of grade 3/4 thrombocytopenia by cycle for patients receiving panobinostat triplet therapy in the PANORAMA-1 study



Denominator for each cycle based on number of patients at risk

San Miguel et al 2014[97]

Figure 34 Median platelet count compared with baseline over time for the panobinostat and control groups in the PANORAMA-1 study.



BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; PBO, placebo.

Grade 3/4 neutropenia was reported in approximately one-third of patients who received panobinostat triplet therapy, but febrile neutropenia was rare

Grade 3/4 neutropenia was reported by a higher proportion of patients receiving panobinostat than those receiving placebo (34% versus 11%) although few patients in either treatment group reported febrile neutropenia (panobinostat, 1.0%; control, 0.5%). One patient (0.3%)

discontinued owing to grade 3/4 neutropenia in the panobinostat arm compared with none in the placebo arm.

Grade 3/4 neutropenia was managed with dose adjustment or study drug interruption (panobinostat, 10%, n = 37; control, 2%, n = 8). Colony-stimulating factors (granulocyte-colony-stimulating factor or granulocyte-macrophage colony-stimulating factor) were used in 13% and 4% of patients in the panobinostat and placebo groups, respectively.

Few patients in either group discontinued therapy because of infections

Grade 3/4 infections were reported in 31% of patients receiving panobinostat and 24% of those in the control group.[25] These included pneumonia (panobinostat, 17.1%; control, 12.7%), lower respiratory tract infection (panobinostat, 3.1%; control, 2.1%), lung infection (panobinostat, 1.3%) and pneumonitis (control, 1.3%). Most cases of pneumonia or sepsis required hospitalization. However, patients rarely discontinued treatment because of infections (5.0% of patients in the panobinostat group and 3.7% of patients in the control group) and few patients in either group died due to infections (panobinostat, 2.6%; control, 1.6%). Most fatal infection events were associated with myelosuppression.

No clinically significant cardiac-related effects were observed

QT interval prolongation and changes in the ST segment or T-waves are considered a class effect of HDAC inhibitors. In PANORAMA-1, local and central electrocardiogram (ECG) analysis revealed few instances of prolonged QT interval corrected for heart rate by use of Fridericia's QT formula (QTcF). No cases of QTcF above 500 ms were reported in the panobinostat group, whilst two patients experienced this in the control group. Few patients in either group had a QTcF increase greater than 60 ms above baseline (three in the panobinostat group and four in the control group). T-wave changes (panobinostat, 40% of patients; control, 18%) and ST–T segment changes (panobinostat, 22% of patients; control, 3%) although more common in the panobinostat group, were considered to be asymptomatic.

The incidence of ischaemic heart disease was low in both treatment groups (any grade: panobinostat, 3.7%; control, 1.3%); thus panobinostat is unlikely to increase the risk of ischaemic heart disease.[25]

Few deaths occurred over the course of the PANORAMA-1 study and were from a variety of causes

Over the course of the study (during treatment and the month following the end of treatment), there were 30 (8%) deaths in the PANO/BTZ/DEX group and 18 (5%) in the placebo/BTZ/DEX group.[9] Of these deaths, four in the panobinostat group and six in the placebo group were due to progressive disease. In the panobinostat group, 11 (2.9%) deaths

were judged to be possibly related to study treatment by the investigator. The causes of these 11 deaths were infection (n = 7), haemorrhage (n = 2), myocardial infarction (n = 1) and cerebrovascular accident (n = 1). In the placebo group, seven deaths (1.9%) were judged to be possibly related to treatment; the events were infection (n = 4), haemorrhage (n = 1), pulmonary embolism (n = 1) and cardiac arrest (n = 1). In both groups approximately half of the deaths occurring during treatment occurred during the first two cycles of therapy.[25] During the post-treatment period there were fewer deaths in the panobinostat group (36% versus 45%)..

The overall risk of grade 3/4 adverse events was similar in elderly and younger patients

In the PANORAMA-1 study, 42% of patients were aged 65 years or older. Analysis of the relative risk of grade 3/4 adverse events and serious adverse events found that the risk was similar for both younger and older patients.[25] However there was a trend toward a higher relative risk for death on treatment, and for specific grade 3/4 adverse events, namely haemorrhage, thrombocytopenia, diarrhoea and fatigue. This was further confirmed in an analysis of risk factors for toxicity which found age ≥ 65 years and a low baseline platelet count (< 150 x 10^9/l) to be associated with an increased risk for toxicity.

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 Efficacy

The clinical efficacy and safety of panobinostat in combination with BTZ/DEX in patients with rrMM have been demonstrated in the pivotal phase 3 RCT, PANORAMA-1, and further supportive data are provided by the single-arm phase 2 study, PANORAMA-2.

Panobinostat plus BTZ/DEX provided a clinically meaningful extension of PFS to 12 months

In the PANORAMA-1 study, panobinostat plus BTZ/DEX provided a clinically meaningful extension of PFS to 12 months (from 8.1 months, $p < 0.0001$) and reduced the risk of progression by 37% versus BTZ/DEX. This benefit was achieved regardless of patient baseline characteristics, whether patients had relapsed or relapsed and refractory disease, or prior number or type of therapy, and was confirmed in all sensitivity analyses performed. Furthermore, the median PFS observed for BTZ/DEX was consistent with that previously reported for bortezomib in patients with rrMM.[12-15] The statistically and clinically significant 4-month prolongation in PFS achieved with panobinostat triplet therapy is particularly impressive in that most patients would have received prior therapy with the highly effective current standards of care − bortezomib, lenalidomide or thalidomide − and over half of patients had received two or three prior lines of therapy. This is in contrast to the pivotal trials for bortezomib and lenalidomide, performed approximately a decade ago, when patients had only received chemotherapy and possibly thalidomide (eg 50% of patients in APEX;[20] 38% of patients in MM-009/010[93]) prior to study treatment.

- Furthermore, the improvement in PFS was robust and clinically relevant for the following reasons:
- The improvement in PFS was consistent across all pre-planned sensitivity analyses, with HRs ranging between 0.58 and 0.71 and all were highly statistically significant ($p < 0.0001$). In particular, the PFS benefit was consistent when using various censoring methods, the Independent Review Committee (IRC) assessment, the Per Protocol set, or a Cox model adjusting for baseline covariates. In addition, a similarly high level of consistency was observed in the pre-specified subgroup analyses, demonstrating patient benefit independent of age group (< and ≥ 65 years), gender, race, prior therapies (ie, bortezomib, IMiDs, stem cell transplantation), relapsed or relapsed-and-refractory disease, and cytogenetic risk.
- The improvement in PFS was associated with an improvement in the quality of responses. While the overall response rate (ORR, ≥ PR) was only slightly higher among patients in the panobinostat group relative to the control group (60.7% versus

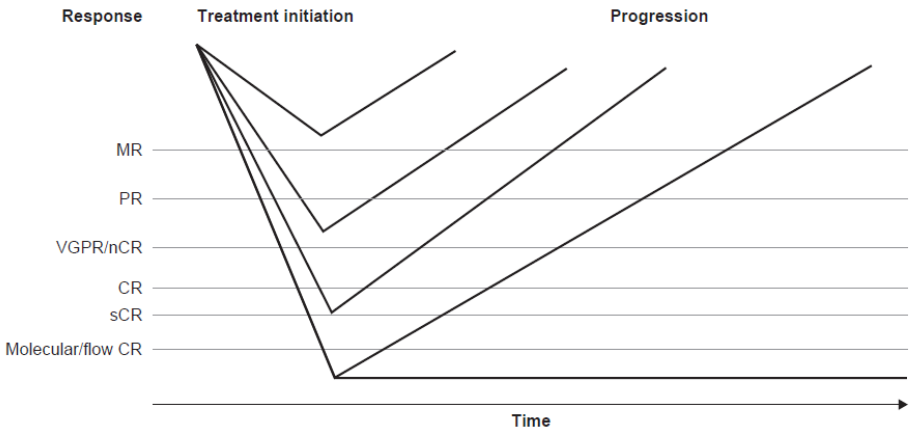
54.6%, respectively), it was associated with a marked increase in the rate of near complete response or complete response (nCR/CR, 27.6% versus 15.7%). This is particularly relevant given that higher quality responses (> PR) have been shown to be associated with longer PFS and OS in patients with relapsed or refractory MM.[16,17] Accordingly, in landmark analyses, the achievement of a response > PR was associated with prolonged PFS.

- The improvement in PFS was also associated with longer duration of response (13.14 months versus 10.87 months) and in particular the duration of CR/nCR (18.43 months versus 14.52 months). This may be relevant given the significantly longer PFS (associated with PANO/BTZ/DEX versus BTZ/DEX) despite the fact that a similar ORR was achieved in both treatment arms.
- The improvement in PFS was also associated with a trend towards an improvement in OS. At the second interim OS analysis when 86.5% of the 415 target final OS events had occurred, median OS was 38.24 months and 35.38 months, in the panobinostat and control groups, respectively (HR 0.87; 95% CI: 0.70 to 1.07; p = 0.18). A total of 342 patients (panobinostat group, n = 179; control group, n = 163) are still being followed for survival. Importantly, crossover of patients between the treatment arms was not allowed to preserve the integrity of this endpoint.

Panobinostat plus BTZ/DEX improved the quality of response to treatment

PANO/BTZ/DEX improved the quality of response to treatment, with 28% of patients achieving a CR or nCR compared with 16% of patients receiving BTZ/DEX, and prolonged the duration of response.[9] This is of particular significance as achieving at least a PR has been shown to be associated with improved PFS and OS (Figure 35),[16,17] and indeed a landmark analysis of data from the PANORAMA-1 study revealed a statistically significant prolongation of PFS for patients achieving a nCR/CR with PANO/BTZ/DEX compared with those achieving a PR.[18] Furthermore, achieving a deeper quality of response [CR versus VGPR or PR] has been shown to be associated with a longer TFI in patients receiving BTZ/DEX.[19]

Figure 35 Correlation between response and time to progression



CR, complete response; MR, minimal response; nCR, near-complete response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
Chanan-Khan and Giralt, 2010 #651;Niesvizky et al 2008 #631;Harousseau et al. 2009 #662}[17,19,124]

Panobinostat triplet therapy extended the TFI by 4.5 months in patients achieving a CR/nCR.

Panobinostat triplet therapy also extended the TFI (ie, the period from completion or discontinuation of therapy to the resumption of therapy on disease progression) by 3.6 months (from 3.9 months for BTZ/DEX to 7.5 months for PANO/BTZ/DEX) in the overall population and by 4.5 months in patients achieving a CR/nCR. This is in contrast to the situation with the current standards of care, other than following a stem cell transplantation, where the duration of the TFI achieved can be limited, as discussed in section 4.7.4 (see Figure 18). Furthermore, the duration of exposure to BTZ/DEX and the associated PFS in the control group were consistent with those seen in previous studies suggesting that the improved TFI associated with panobinostat is a true reflection of the treatment benefit provided by panobinostat rather than an anomaly of the PANORAMA-1 trial (Figure 17)

The prolonged TFI observed with panobinostat triplet therapy is expected to have a significant impact on HRQL given that patients are likely to be free from symptoms and from the adverse events associated with treatment during the TFI. Indeed a survey of UK patients with MM found that prolongation of the TFI was associated with significant improvements in specific aspects of HRQL and that HRQL was greatest for patients in the first TFI compared with during active treatment (see section 3.2).[23] The reported extension to the TFI is also consistent with an analysis of data from the pivotal phase 3 trial for bortezomib which reported a longer TFI in patients achieving a CR compared with those achieving a VGPR or PR;[19] thus the prolongation of TFI observed with panobinostat in PANORAMA-1 may well reflect the deeper responses achieved with PANO/BTZ/DEX over BTZ/DEX.

Survival data for the study are not yet mature enough to allow a final analysis, but interim OS data (as of 18 August 2014) show a numerical superiority for PANO/BTZ/DEX over BTZ/DEX.

Panobinostat triplet therapy can benefit patients refractory to both bortezomib and IMiDs

The results from PANORAMA-1 are supported by those for the PANORAMA-2 study, which demonstrated benefits for panobinostat triplet therapy in heavily pre-treated patients who were refractory to bortezomib (almost all patients had also received lenalidomide and two-thirds had received thalidomide). Moreover, a further analysis of data from the PANORAMA-2 study showed that patients who achieved at least a PR on panobinostat therapy had an improved median PFS and OS over patients who did not.[24] In this study at least a PR was achieved in 35% of patients and median OS was 17.5 months. This compares favourably to the best ORR of 24% and median OS of 9 months reported for a similar patient population (refractory to bortezomib and IMiDs) with a median of four prior therapies who received various therapies.[14] These results thus indicate that the panobinostat regimen can benefit patients refractory to both bortezomib and IMiDs, a patient population for whom there are very few effective options.

In conclusion, the results of the PANORAMA-1 and -2 studies indicate that the addition of panobinostat to BTZ/DEX improves the outcomes for patients with rrMM. For patients with rrMM for whom bortezomib -based therapy is indicated, the addition of panobinostat significantly improves PFS and can be expected to improve HRQL given the higher proportion of patients who achieve a deeper response to therapy and the prolonged TFI provided by this regimen. For patients with more advanced disease who are refractory to prior bortezomib, the addition of panobinostat can also provide clinically significant benefits by restoring sensitivity to bortezomib.

4.13.2 Safety

Panobinostat triplet therapy was generally well tolerated with a predictable and manageable safety profile

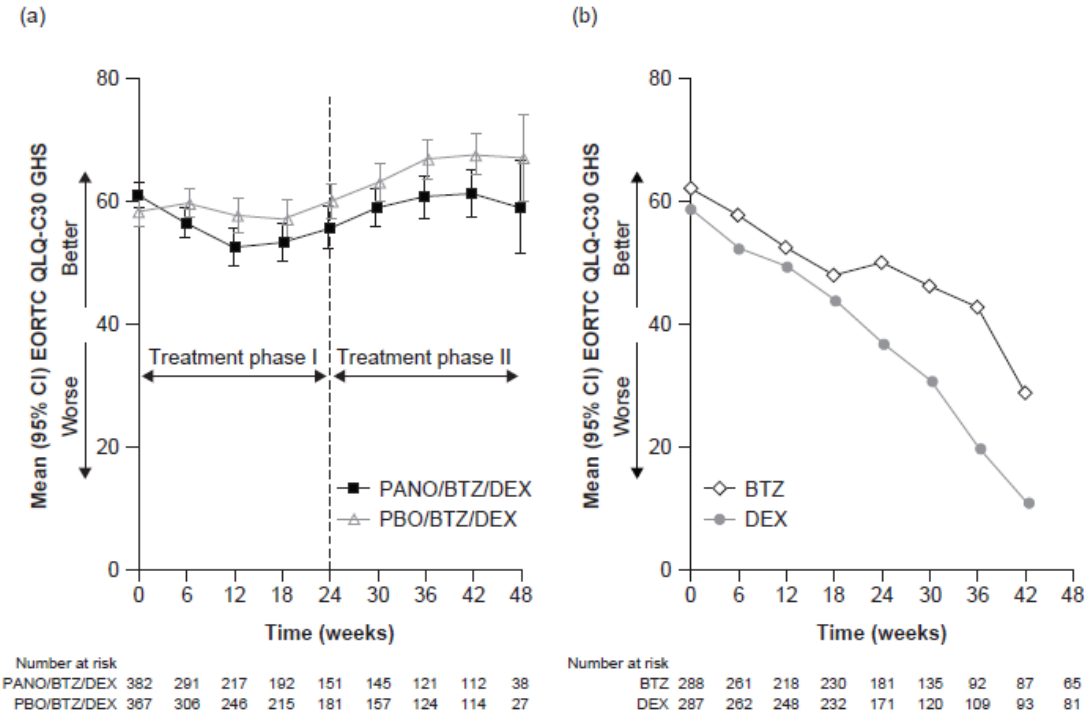
In both studies, panobinostat triplet therapy was generally well tolerated with a predictable and manageable safety profile. Diarrhoea, asthenia and fatigue were the most frequently reported non-haematological grade 3/4 adverse events associated with panobinostat triplet therapy in the PANORAMA-1 study. Diarrhoea was managed by dose adjustment or interruption and anti-diarrhoeal medication, and few patients discontinued treatment owing to diarrhoea, asthenia or fatigue of any grade. Furthermore, panobinostat triplet therapy was not associated with an increased risk of grade 3/4 peripheral neuropathy versus BTZ/DEX. Thrombocytopenia was the most frequently reported grade 3/4 haematological adverse event associated with panobinostat triplet therapy, but was reversible, non-cumulative and rarely led

to treatment discontinuation; furthermore, the rate of grade 3/4 haemorrhages was low (4%). Grade 3/4 neutropenia was reported in approximately one-third of patients who received panobinostat triplet therapy but febrile neutropenia was rare. Rates of discontinuation due to adverse events and the incidence of on-treatment deaths with PANO/BTZ/DEX were within the ranges reported for current standards of care, namely bortezomib-based, lenalidomide-based regimens, but were higher than in the BTZ/DEX group (36% versus 20%). Diarrhoea was the adverse event most frequently leading to discontinuation in the panobinostat group but lead to discontinuation in only 4.5% of patients. The safety profile observed in the PANORAMA-2 study was in general agreement with that reported for the PANORAMA-1 study, except for a noticeably lower incidence of grade 3/4 sepsis in both treatment groups in the PANORAMA-1 study, possibly reflecting better management of this adverse event in the phase 3 study (PANORAMA-1 panobinostat group, 7%; PANORAMA-1 BTZ/DEX, 4%; PANORAMA-2, 15%).[25]

Subcutaneous administration of bortezomib is likely to improve the safety profile observed for panobinostat triplet therapy in routine clinical practice

In both PANORAMA-1 studies, bortezomib was administered intravenously. In the UK (and in most countries), there is a tendency for bortezomib being administered subcutaneously following demonstration that the subcutaneous route is better tolerated and provides equivalent efficacy to iv administration. In particular, a phase 3 trial comparing intravenous and subcutaneous administration demonstrated a lower incidence of the following grade 3/4 adverse events of at least 5%: neuralgia (3% subcutaneous versus 9% intravenous), peripheral neuropathy (6% subcutaneous versus 15% intravenous), neutropenia (13% subcutaneous versus 18% intravenous) and thrombocytopenia (8% subcutaneous versus 16% intravenous).[26] A reduced frequency of intravenous administration of bortezomib has also been shown to improve tolerability, resulting in lower incidences of peripheral neuropathy, gastrointestinal toxicities and thrombocytopenia.[27] Consistent with this, a reduction in the incidence of new or worsening grade 3/4 adverse events was observed in PANORAMA-1 during the second treatment phase when bortezomib was administered once rather than twice weekly. These observations suggest that the incidence of grade 3/4 adverse events observed with the panobinostat regimen in routine clinical practice is likely to be lower than that reported in the PANORAMA-1 study if bortezomib is administered subcutaneously, and that toxicities can be effectively managed by dose reductions. Furthermore, over the period since the introduction of bortezomib into routine clinical practice, management of adverse events has improved with the gain in clinical experience. This is probably reflected in the difference in HRQL reported for the bortezomib group in the APEX trial and PANORAMA-1. In the APEX trial, EORTC QLQ-C30 GHS scores for the bortezomib treatment group declined markedly during treatment,[108] whereas in PANORAMA-1, scores remained relatively constant during the first treatment phase and improved in the second treatment phase when bortezomib was administered once, rather than twice, weekly (Figure 36).

Figure 36 Scores for EORTC QLQ-C30 GHS reported in a) the PANORAMA-1 study and b) the APEX trial



BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; EORTC QLQ-C30 GHS; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – C30, Global Health Status; PANO, panobinostat; PBO, placebo.
FDA 2014;[25] Lee et al. 2008[108]

4.13.3 Strengths of the evidence base

The clinical evidence base for panobinostat triplet therapy, PANO/BTZ/DEX, has a number of strengths. First, the primary evidence for the efficacy of PANO/BTZ/DEX comes from a large, multicentre, international RCT involving 768 patients randomised 1:1 to PANO/BTZ/DEX or BTZ/DEX (PANORAMA-1). This study included a broad spectrum of patients including those with relapsed or relapsed and refractory disease, and patients who had received multiple lines of prior therapy. Secondly, the primary endpoint of this study was PFS, which is widely regarded as the most appropriate endpoint for clinical trials of treatments for onco-haematological indications. A further quality control measure underpinning the robustness of this study was that PFS was determined from both investigator assessments and independent assessments and both values were in good agreement. Thirdly, responses were assessed at 3-week intervals during treatment and 6-weekly thereafter till progression, and confirmed six weeks after the initial assessment, thus providing a robust measure of treatment response throughout the study. Fourthly, patients enrolled in the PANORAMA-1 study were broadly

representative of patients likely to receive PANO/BTZ/DEX in routine clinical practice in England and Wales, except that the median age of patients was somewhat lower than that observed in routine clinical practice in the UK. Fifthly, the trial is in general reflective of the emerging clinical practice in the England and Wales in that: 1) patients enrolled in the study were broadly representative of patients likely to receive BTZ/DEX with or without panobinostat in clinical practice; 2) the comparator (BTZ/DEX) was given mainly as a second-line treatment regimen in line with the NICE guidance TA129 and current NCDF policies (including the recent delisting of bortezomib as re-treatment as an option) ; 3) thalidomide or bortezomib together with an alkylating agent and a corticosteroid are the approved first-line treatment options for transplant ineligible patients as per NICE guidance TA228; 4) lenalidomide is not yet approved for reimbursement as first-line therapy; 5) BTZ/DEX with or without thalidomide is the recommended induction regimen for transplant eligible patients (see sections 3.3 and 3.5).

4.13.4 Weaknesses of the evidence base

The evidence base for PANO/BTZ/DEX has a number of weaknesses largely relating to the design of the PANORAMA-1 study.

First, OS data for this study are not yet mature. OS data, as of 18 August 2014, although showing a numerically superior difference between treatment groups in favour of the PANO/BTZ/DEX arm, have not demonstrated a statistically significant survival benefit for panobinostat triplet therapy. However, a trend toward significance has been observed based on the difference in OS between treatment groups in the analysis performed for the data cut-off of 10 September 2013 (p = 0.26) and the updated analysis performed for the data cut-off of 18 August 2014 (p = 0.178).

Second, in both the PANORAMA-1 and PANORAMA-2 trials bortezomib was administered intravenously. It is now well established that subcutaneous delivery of bortezomib is better tolerated without loss of efficacy.[13] The NHS in England and Wales does still administer bortezomib by intravenous injection in line with historical licensing guidelines, but it is now more commonly administered subcutaneously as recommended by BCSH guidelines.[125] Given the improved safety profile of subcutaneous bortezomib, this methodological change is anticipated to improve the safety profile of panobinostat triplet therapy significantly, and means that the existing safety data for panobinostat triplet therapy do not reflect the likely clinical experience.

Third, HRQL data as assessed by the EQ-5D are not available for the PANORAMA-1 study. HRQL was assessed during treatment in the PANORAMA-1 trial using the EORTC QLQ-C30 and the myeloma-specific instrument − the EORTC QLQ-MY20 − and the possible impact of neurotoxicity was assessed using the FACT FACT/GOG-Ntx, thus providing a detailed

assessment of the impact of treatment on patients. However, these assessments were not continued after treatment discontinuation. Given that HRQL has been shown to be highest in the TFI and the observation that panobinostat triplet therapy is associated with a prolongation of the TFI, the available HRQL data from PANORAMA-1 do not provide a realistic measure of the likely HRQL benefit associated with the addition of panobinostat to BTZ/DEX.

4.13.5 Relevance of the evidence to the decision problem

Evidence from PANORAMA-1 is directly relevant to the decision problem as most aspects of study generally correspond to routine clinical practice in England and Wales. Firstly, patient selection criteria used in the PANORAMA-1 study (as detailed in section 4.3.2), are likely to correspond to those used for selecting patients for treatment with panobinostat triplet therapy in routine clinical practice. Indeed, the study included 30 patients from six centres in the UK. Secondly, the comparator (BTZ/DEX) used in the PANORAMA-1 study is directly relevant to clinical practice in the UK, where it is given as second-line treatment in 91% and as third-line therapy in 11% of patients with rrMM in England. Thirdly, both the PANORAMA-1 and PANORAMA-2 studies are for the licensed dose of panobinostat and for the licensed regimen. Fourthly, the assessment of response to therapy used in this study is comparable to that used in routine clinical practice in the UK (although the IMWG rather than EBMT criteria are generally used in clinical practice). Fifthly, PFS and TFI are relevant measures of patient benefit, particularly as the TFI is likely to be associated with an improved HRQL compared with that observed during treatment or disease progression. Taken together, these highlighted outcomes demonstrate that the evidence derived from this comparative study is directly translatable to patient clinical benefit in a UK setting and is thus relevant to the decision problem.

However, there is a notable difference between the way bortezomib was administered in PANORAMA-1 compared with current UK practice. Bortezomib was administered to patients in eight 3-week cycles (treatment phase 1) and patients who achieved at least no change (at day 1 of cycle 8) then entered phase 2 to receive four 6-week cycles. In contrast, according to the NICE guidance on bortezomib monotherapy as a second-line treatment in rrMM (TA129), the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in people who have a CR or a PR (ie, a reduction in serum M protein of 50% or more or, where serum M protein is not measurable, an appropriate alternative biochemical measure of response) and the manufacturer rebates the full cost of bortezomib for people who, after a maximum of four cycles of treatment, have less than a PR (as defined above). The use of bortezomib in the PANORAMA studies thus does not correspond exactly with that recommended in current NICE guidance and means that the efficacy outcomes for the BTZ/DEX group in PANORAMA-1 may be better than those achieved in routine practice. Thus PANORAMA-1 is likely to provide a conservative estimate

of the benefit for the addition of panobinostat to BTZ/DEX, as given in routine practice in England and Wales.

4.13.6 End-of-life criteria

As summarised in Table 36, panobinostat for treatment of rrMM meets the criteria for being a life-extending treatment at the end of life (see sections 3.4 and 4.7.6 for further details).

Table 36 End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Data from the HMRN in relation to a cohort of 1645 MM patients diagnosed between September 2004 and August 2011, reported that a median OS was 1.2 years from the start of second-line treatment, and 1.4 years when the second-line treatment was a bortezomib-based regimen (see section 3.4).[60]
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	OS data from the PANORAMA-1 trial are not yet mature but the most recent analysis, reported a median OS of 38.24 months for the PANO/BTZ/DEX group and 35.38 months for the PBO/BTZ/DEX group, corresponding to 2.86 months ($p = 0.1783$)[25] (see section 4.7.6)
The treatment is licensed or otherwise indicated for small patient populations	Approximately 1300 patients in England and Wales would be eligible to receive panobinostat annually (see section 3.4)

BTZ, bortezomib; DEX, dexamethasone; HMRN, Haematological Malignancy Research Network; MM, multiple myeloma; NHS, National Health Service. OS, overall survival; PANO, panobinostat; PBO, placebo

4.14 Ongoing studies

Both the PANORAMA-1 and PANORAMA-2 studies are ongoing and designed to observe patients for OS outcomes. The manufacturer anticipates that during the course of the appraisal, additional data will become available from the PANORAMA-1 study, with OS data anticipated in May/June 2015.

Data may also become available from the following ongoing studies that are assessing panobinostat in rrMM:

- safety data from a UK phase 1/2 study of BTZ/THAL/DEX/PANO followed by panobinostat maintenance therapy for up to 1 year (NCT02145715)
- an international dose-escalation/maximum tolerated dose phase 1b study of PANO/BTZ (NCT00532389)
- an open-label expanded treatment programme of BTZ/DEX/PANO performed in the USA (NCT02204553).

5 Cost effectiveness

5.1 Published cost-effectiveness studies

5.1.1 Identification of studies

A systematic review was performed in August 2013 to identify economic evidence relating to second-line therapy of patients with rrMM. Updates to the review were performed on 24 April 2014 and 3 to 9 December 2014. The search aimed to identify cost-utility studies of treatments for rrMM together with cost analysis studies and resource use studies relating to patients with MM for the following interventions: panobinostat, thalidomide, lenalidomide, bortezomib, pomalidomide, carfilzomib and ixazomib. Specific inclusion and exclusion criteria were utilized to identify relevant references. Two analysts independently screened each reference for inclusion based on title and abstract. A third researcher resolved any differences between results. All publications that met entry criteria for the review were obtained as full articles and reassessed against the review criteria. Data from the selected studies were subsequently used to populate predefined summary tables. All data were fully checked by the third analyst. Further details of the methodology for the reviews are provided in Appendix 11.

To be included in this systematic review, references had to meet the inclusion criteria (and none of the exclusion criteria) detailed in Table 37.

Table 37 Eligibility criteria used in the screening

Variable	Inclusion criteria	Exclusion criteria
Populations	Patients with rrMM, receiving treatment with an intervention of interest for CUA studies Patients with MM for cost analysis and resource use studies	CUA where rrMM-specific results cannot be clearly separated from other data
Interventions	Panobinostat Thalidomide Lenalidomide Bortezomib Pomalidomide Carfilzomib Ixazomib	Specific first-line therapies or ASCT
Outcomes	Study must contain at least one of the following: ICERs cost per clinical outcome total QALYs total LYGs total costs costs reported as an outcome	
Study design	Cost utility Cost effectiveness Cost consequence Cost/resource use	Studies with only clinical outcomes
Publication type	Primary paper Abstract HTA review Systematic review Published from March 2013 to April 2014	Published before March 2013 Editorial Review Letter Reference included in original systematic review
Language restrictions	English	Non-English languages

ASCT, autologous stem cell transplantation; CUA, cost–utility analysis; HTA, health technology assessment; ICER, incremental cost effectiveness ratio; LYG, life-years gained; MM, multiple myeloma; QALY, quality-adjusted life-year; rr, relapsed/refractory.

5.1.2 Description of identified studies

In total 14 cost-utility studies were identified in the systematic review and updates. Seven of these were described in detail in full papers or health technology assessment (HTA) submissions and were reviewed in detail and are summarised in Table 38 (see Appendix 12 for a quality assessment of these studies).The model structure of the de novo model (described in section 5.2.2) was informed by a review of the previous modelling approaches.

Table 38 Summary list of other cost-effectiveness evaluations.

Study	Year	Country(ies) where study was performed	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
HTA 2007[88] (Green et al, 2009[126])	2007	England and Wales	Semi-Markov state transition model	NR	NR	BTZ versus HiDEX: £38,000
Hornberger et al, 2010[127]	2010	Sweden	Partitioned survival model	BTZ versus HiDEX: 0.04 BTZ versus LEN/DEX: 0.69	BTZ versus HiDEX: SEK 902,874 BTZ versus LEN/DEX: cost-saving	BTZ versus HiDEX: SEK 662,621 BTZ versus LEN/DEX: dominant
Moller et al, 2011[128]	2011	Norway	Discrete event simulation model	LEN/DEX versus BTZ: 0.76	LEN/DEX versus BTZ: NOK188,245	LEN/DEX versus BTZ: NOK247,048
NICE HTA 2009[87]	2009	England and Wales	Partitioned survival model	LEN/DEX versus BTZ (if 1 prior therapy): NR LEN/DEX versus DEX (if ≥ 2 prior therapies): 1.86 LEN/DEX versus DEX (if 1 prior therapy, THAL): 1.7	LEN/DEX versus BTZ (if 1 prior therapy): NR LEN/DEX versus DEX (if ≥ 2 prior therapies): NR LEN/DEX versus DEX (if 1 prior therapy, THAL): NR	LEN/DEX versus BTZ (if 1 prior therapy): £46,865 LEN/DEX versus DEX (if ≥ 2 prior therapies): £30,350[b] LEN/DEX versus DEX (if 1 prior therapy, THAL): £28,941[b]
Brown et al, 2013[129]	2013	England and Wales	Individual simulation model	LEN/DEX versus DEX in patients who have received 1 prior therapy: 2.2	LEN/DEX versus DEX in patients who have received 1 prior therapy: £66,483	LEN/DEX versus DEX in patients who have received 1 prior therapy: £30,153
Fragoulakis et al, 2013[130]	2013	Greece	Discrete event simulation model	LEN/DEX versus BTZ: 0.79	LEN/DEX versus BTZ: €30,402	LEN/DEX versus BTZ: €38,268

NICE HTA 2014[131]	2014	England and Wales	Partitioned survival model	POM/LoDEX versus BTZ/DEX: 0.61 POM/LoDEX versus CTD: 0.61 POM/LoDEX versus BTD: 0.61	POM/LoDEX versus BTZ/DEX:£30,782 POM/LoDEX versus CTD: £47,219 POM/LoDEX versus BTD: £44,142	POM/LoDEX versus BTZ/DEX: £50,366 POM/LoDEX versus CTD: £77,915 POM/LoDEX versus BTD: £72,250

BTD, bendamustine plus thalidomide and dexamethasone; BTZ, bortezomib; CTD, cyclophosphamide plus thalidomide and dexamethasone; DEX, dexamethasone; HiDEX, high dose dexamethasone; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LoDEX, low dose dexamethasone; NICE, National Institute for Health and Care Excellence; NR, not reported; POM, pomalidomide; QALY(s), quality-adjusted life year(s); THAL, thalidomide.

5.2 De novo analysis

5.2.1 Patient population

The model described in the submission considers a patient population which corresponds to the full cohort included in the PANORAMA-1 trial which enrolled patients with rrMM who had received one to three previous treatments (n = 768) (see section 4.5 and Table 10). This population is considered to be largely representative of patients likely to be eligible to receive panobinostat triplet therapy as a second-line option in clinical practice in the UK. A more restricted patient population (ie patients having received after at least two prior lines of treatment, including an IMiD and bortezomib, as described in section 4.8.2) is also considered and are described in Appendix 17.

5.2.2 Model structure

A decision analytic semi-Markov model was developed having the structure shown in Figure 37. The model captures three key aspects of MM that are affected by disease progression and the effects of treatment, namely survival, HRQL and costs. The health states in the model are identical to those used in previous recent models submitted for NICE technology appraisals.[52,87,131] Disease progression is implemented through patients moving from the two pre-progression health states to the post-progression health state, corresponding to therapy with LEN/DEX, and then to the post-progression health state, corresponding to fourth-line therapy, that is POM/DEX together with further supportive care (Medical Resource Utilisation, MRU)[7], or other active treatments together with further supportive care, or supportive care alone, and finally to the death health state. The modelled fourth-line treatment options are referred to as last line of treatment (LLoT).

The model consists of three key health states: pre-progression, post-progression, and death. Two pre-progression health states are included, one corresponding to when a patient is receiving treatment (Health state A, pre-progression, on treatment) and a second (Health state B, pre-progression, off treatment) corresponding to when a patient is progression-free but receives no treatment. These two health states have been considered in two recent NICE HTA submission models,[87,131] and enable the model to capture the utility and resource use implications of being on or off treatment. Two post-progression states are also included to capture patients receiving different subsequent lines of antineoplastic treatments which are assumed to be LEN/DEX as third-line therapy as recommended by current NICE guidance[87]

[7] Medical-resource utilisation incorporates clinical attendance, inpatient admissions, transfusions, supportive therapy, blood tests as described by ASH 1727, Gooding et.al.

(Health state C), and POM/DEX or other active treatments and/or supportive care as LLoT[51,79,89] (Health state D).

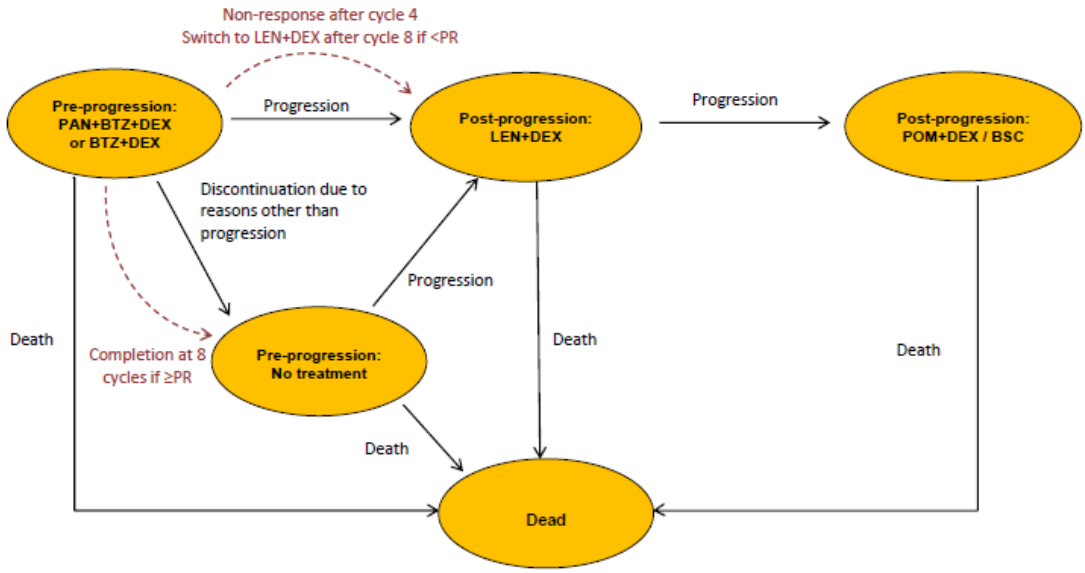
The model structure corresponds to the expected clinical pathway for management of patients with rrMM. Broadly, patients receive the initial treatment (PANO/BTZ/DEX or BTZ/DEX) until disease progression or discontinuation for other reasons and then progress to receive LEN/DEX, as per current NICE guidance[87] and UK treatment guidelines.[51] On progression on LEN/DEX patients proceed to receive LLoT, and patients may die at any time. However the treatment pathway differs according to the initial treatment.

Patients entering the model can receive PANO/BTZ/DEX or BTZ/DEX. Patients receiving PANO/BTZ/DEX may discontinue treatment early due to progression or relapse or due to reasons other than progression. In line with current UK clinical guidelines[51] and clinical practice, those who discontinue treatment due to progression or relapse or have not achieved a PR[79] will receive LEN/DEX, while those who discontinue treatment due to reasons other than progression and have at least a PR stop treatment and remain off treatment until they experience progression. At this point they then receive LEN/DEX. Patients who progress on LEN/DEX then receive LLoT until death. Patients are at risk of dying at any time in the model and can move to the Death health state from any other health state.

Patients receiving BTZ/DEX follow the same treatment pathway as patients receiving PANO/BTZ/DEX for the first four cycles (ie may discontinued early due to progression or other reasons). At the end of cycle 4, patients still on treatment are evaluated for response (as per the patient access scheme approved by TA129[88]) and patients who have achieved at least a PR continue on BTZ/DEX whereas those who have not achieved at least a PR discontinue BTZ/DEX and initiate therapy with LEN/DEX. Patients who are off treatment at the end of cycle 4 are not subject to response evaluation. Those who continue on BTZ/DEX may discontinue therapy due to progression or due to reasons other than progression. 90% of the patients still on BTZ/DEX at the end of cycle 8 will stop the treatment, as per the bortezomib label. Those with at least a PR will remain off-treatment until disease progression, while those with less than a PR will initiate therapy with LEN/DEX. A minority of the patients (10%) completing eight cycles of BTZ/DEX are allowed to continue on BTZ/DEX until progression or discontinuation due to other reasons up to cycle 16, as per the PANORAMA-1 protocol. (It is worth noting that the efficacy data presented for the control arm is based on the PANORAMA-1 trial that did not require patients to discontinue therapy for either of the above conditions.) Those who progress on LEN/DEX then receive LLoT until death and patients are at risk of dying at any time.

Key features of the model are summarised in Table 39.

Figure 37 Structure of the decision analytic semi-Markov model



Red arrows apply only to patients who receive BTZ/DEX.

Patients who complete PAN/BTZ/DEX treatment transition to the 'Pre-progression, No treatment health state'.

BSC, best supportive care; BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PAN, panobinostat; POM, pomalidomide; PR, partial response.

Table 39 Key features of analysis.

Factor	Chosen value	Justification	Flexibility	Reference
Time horizon	25 years	Appropriate timescale for evaluating conditions with high death rates such as rrMM, to enable capturing (differential) costs and outcomes	Flexibility includes time horizons ranging from “trial period” to 25 years	
Cycle length	3 weeks	Reflects the drug administration schedule in the PANORAMA-1 trial	Fixed	San Miguel et al, 2014[9]
Half-cycle correction	Applied	Consistent with previous economic models and the NICE Guide to the methods of technology appraisals	Fixed	NICE technology appraisals for BTZ, LEN and POM[52,87,131]; Guide to the methods of technology appraisals[132]
Were health effects measured in QALYs; if not, what was used?	Lys and QALYs	Consistent with previous economic models and the NICE Guide to the methods of technology appraisals	Outcomes such as “Life years gained” and “Time spent off-treatment” are presented	NICE technology appraisals for BTZ, LEN and POM[52,87,131]; Guide to the methods of technology appraisals[132]
Discounting	Effects: 3.5% Costs: 3.5%	Consistent with the NICE Guide to the methods of technology appraisals	Flexible: any values can be implemented	Guide to the methods of technology appraisals[132]
Analysis perspective	Healthcare system (NHS/PSS)	Consistent with the NICE Guide to the methods of technology appraisals	Direct costs are included, Option to include indirect costs	Guide to the methods of technology appraisals[132]

BTZ, bortezomib; LEN, lenalidomide; LY(s), life year(s); NHS, National Health Service; NICE, National Institute for Health and Care Excellence; POM, pomalidomide; PSS, personal social services; QALYs, quality-adjusted life years; rrMM, relapsed/refractory multiple myeloma.

5.2.3 Intervention technology and comparators

In the model, the intervention, PANO/BTZ/DEX, is implemented as per the anticipated marketing authorisation and is given according to the recommended regimen and that utilized in the PANORAMA-1 trial (see section 4.3). The comparator, BTZ/DEX, is also implemented as per the marketing authorisation and according to the recommended regimen. Thus unlike in the PANORAMA-1 trial, BTZ/DEX is administered for up to eight cycles rather than for 16 cycles as per the trial. However, the model allows a minority of the patients (10%) of those who achieve at least a PR at the end of cycle 8 to continue on BTZ/DEX, as per the clinical trial.

5.3 Clinical parameters and variables

As described above (section 5.2), in the health economic model patients' survival is partitioned into pre-progression and post-progression periods, of which the pre-progression period is further divided into on-treatment and off-treatment intervals. To model the flow of patients through the different health states over time, transition probabilities were estimated by *post-hoc* analyses of patient-level data from the PANORAMA-1 trial or by deriving transition probabilities from external sources (ie the pivotal MM-009 and -010 trials for LEN/DEX[93]). For patients receiving BTZ/DEX different sets of transition probabilities were used corresponding to: 1) cycles 1 to 4: all patients and 2) cycles 5 to 8: responders ie patients with ≥ PR [since patients not responding (ie not achieving PR) after four cycles of therapy have already discontinued BTZ/DEX] 3) cycles 5 to 8: patients who discontinue therapy during cycles 1 to 4 for reasons other than progression or death, 4) cycles 9 and onwards: patients who discontinue therapy during cycles 5 to 8 due to reasons other than progression or death 8. Table 40 summarises the approaches used to derived transition probabilities and their use in the model.

Table 40 Approaches used to derived transition probabilities and their use in the economic model

Parameter	Data source	Model used for base case	Use of transition probabilities
PANO/BTZ/DEX			
Risk of progression or death	PANORAMA-1, PANO/BTZ/DEX Patient-level PFS data	Weibull	Health State A, PANO/BTZ/DEX
Risk of progression (and risk of death)	PANORAMA-1, PANO/BTZ/DEX Patient-level PFS data	Logistic regression with treatment indicator and the log of cycle	Health State A, PANO/BTZ/DEX
Risk of treatment discontinuation	PANORAMA-1, PANO/BTZ/DEX Patient-level data for PFS and treatment exposure	Log-logistic	Health State A, PANO/BTZ/DEX
BTZ/DEX, cycles 1 to 4			
Risk of progression or death	PANORAMA-1 BTZ/DEX Patient-level PFS data	Weibull	Health State A, BTZ/DEX cycles 1 to 4
Risk of progression (and risk of death)	PANORAMA-1 BTZ/DEX Patient-level PFS data	Logistic regression with treatment indicator and the log of cycle	Health State A, BTZ/DEX cycles 1 to 4
Risk of treatment discontinuation	PANORAMA-1, BTZ/DEX Patient-level data for PFS and treatment exposure	Log-logistic	Health State A, BTZ/DEX cycles 1 to 4
BTZ/DEX responders, cycles 5 to 8			
Risk of progression or death	PANORAMA-1 BTZ/DEX responders Patient-level PFS data	Weibull	Health State A, BTZ/DEX cycles 1 to 4
Risk of progression (and risk of death)	PANORAMA-1 BTZ/DEX responders Patient-level PFS data	Logistic regression with treatment indicator and the log of cycle	Health State A, BTZ/DEX cycles 1 to 4
Risk of treatment discontinuation	PANORAMA-1, BTZ/DEX responders Patient-level data for PFS and treatment exposure	Exponential	Health State A, BTZ/DEX cycles 1 to 4
BTZ/DEX, discontinuing treatment during cycles 1 to 4 without disease progression			

Parameter	Data source	Model used for base case	Use of transition probabilities
Risk of progression	PANORAMA-1 BTZ/DEX discontinuers before cycle 4, patient level data for TTP	Exponential[a]	Health State A. BTZ/DEX cycles 5 to 8
Risk of death	PANORAMA-1 BTZ/DEX dicontinuers before cycle 4, patient level data for OS	Exponential[a]	Health State A. BTZ/DEX cycles 5 to 8
BTZ/DEX discontinuing treatment during cycles 5 to 8 without disease progression			
Risk of progression	PANORAMA-1 BTZ/DEX dicontinuers between cycles 5 to 8, patient level data for TTP	Exponential[a]	Health State B. BTZ/DEX cycle 9 onwards
Risk of death	PANORAMA-1 BTZ/DEX dicontinuers between cycles 5 to 8, patient level data for OS	Exponential[a]	Health State B. BTZ/DEX cycle 9 onwards
LEN/DEX			
Risk of progression	Median TTP estimate from the combined MM-009/010 trials	Exponential[a]	Health State C, LEN/DEX
Risk of death	PANORAMA-1 Patient-level OS data for patients who received LEN/DEX after trial regimen, stratified according to whether patients progressed within first 4 cycles or later	Exponential[a]	Health State C, LEN/DEX
Last line of treatment			
Risk of death	PANORAMA-1 Patient-level OS data for patients who received LEN/DEX after trial regimen, stratified according to whether patients progressed within first 4 cycles or later	Exponential[a]	Health State D, LLoT

[a]Chosen to keep model parsimonious

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; LLoT, last line of treatment; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; TTP, time to progression.

Dimopoulos et al 2009[93]

5.3.1 Methodology

For each regimen, survival curves for the risk of progression (or death) were derived from patient-level data (or simulated patient-level data) for PFS. Five parametric survival models (exponential, Weibull, log-logistic, log-normal, Gompertz) were fitted on Kaplan–Meier plots of the individual patient-level PFS data. The regression models were compared visually and were assessed using Akaike information criterion (AIC) and Bayesian information criterion (BIC) to determine their fit to the observed trial data. The best fitting models were also assessed by clinical plausibility and selected for smoothing and extrapolating the PFS data and were used for the base case. For LEN/DEX, to keep the model parsimonious, the patient-level PFS data were assumed to have an exponential distribution.

Applying this approach to PFS data provides an estimate of the risk of progression or death in a given cycle. However, for patients receiving PANO/BTZ/DEX or BTZ/DEX the model required both the risk of progression (to determine how many patients received post-progression treatment) and the risk of death (to determine how many patients died before or upon progression). Therefore in a second step, the proportion of patients who progressed relative to those who had a PFS event was estimated for each cycle by a logistic regression. (Logistic regressions are frequently used to estimate the relative frequency of an event as a function of explanatory variables. The proportion of patients who died was derived from one minus the proportion of patients who progressed.) In the logistic regressions, the relative frequency of progression was explained by the cycle patients experienced the PFS event. Three models were explored:

1. A model with cycle as a continuous explanatory variable (ie one explanatory variable)
2. A model with cycle and cycle squared (ie two explanatory variables)
3. A model with the log of the cycle (ie one explanatory variable).

These models were selected for assessment based on visually inspecting the raw data and suspecting that these models would fit the data fairly well. The best fitting model was selected based on the AIC and BIC criteria.

A similar approach to that described above for risk of progression or death was used to derive transition probabilities for risk of treatment discontinuation (for PANO/BTZ/DEX and BTZ/DEX), based on patient-level data for the duration of treatment from PANORAMA-1.

Transition probabilities for the risk of death in patients receiving LEN/DEX and the subsequent LLoT were derived from patient-level post-progression OS data from PANORAMA-1 for patients who received LEN/DEX as subsequent antineoplastic treatment after PANO/BTZ/DEX or BTZ/DEX. Transition probabilities for LEN/DEX and LLoT were

assumed to be the same for both treatment groups (ie patients initially receiving PANO/BTZ/DEX or BTZ/DEX).

The probability of progression and the probability of death in a) patients discontinuing BTZ/DEX during cycles 1 to 4 without disease progression and b) patients discontinuing BTZ/DEX during cycles 5 to 8 without disease progression were determined by fitting exponential survival curves to Kaplan–Meier plots for TTP and OS for the relevant patient populations from PANORAMA-1.

Where patient-level data were not available from PANORAMA-1 (ie for risk of progression on LEN/DEX) median TTP data was used from a published source.[93]

The sections below provide a detailed description of the patient-level time-to-event data that were used for the estimation of transition probabilities, and the (parametric) survival models from which the transition probabilities were derived.

5.3.2 Clinical input parameters for PANO/BTZ/DEX and BTZ/DEX

Clinical input parameters for PANO/BTZ/DEX and for BTZ/DEX were derived using a similar approach with the exception that for BTZ/DEX parameters were determined separately for cycles 1 to 4 and cycles 5 to 8. This reflects the fact that only patients who achieved a response (≥ PR) by cycle 4 continued to receive BTZ/DEX for cycles 5 to 8 or beyond[8]. Thus parameters for cycle 1 to 4 are derived from patient-level data for the overall population who received BTZ/DEX in PANORAMA-1, whereas parameters for cycles 5 to 8 and beyond[2] are derived from patient-level data for responding patients. Of note, the parameters for cycle 1 to 4 are derived from the entire time period, not just from cycle 1 to 4.

Risk of progression or death

The risk of experiencing a PFS event (ie either progression or death) in a given cycle was estimated using patient-level data from the PANORAMA-1 trial[9]. PFS was the primary outcome of the PANORAMA-1 trial. Time since randomisation until progression or death (ie an event) or censoring was considered as exposure time.
Table 41 provides descriptive statistics for the derived time to PFS event dataset.

[8] 10% of the patients still on treatment with response ≥ PR were allowed to proceed on treatments beyond cycle 8. The remaining 90% of the patients went off-treatment (if at least a PR achieved) or to LEN/DEX (if PR not achieved)

[9] Based on full analysis set, ie patients who were randomised.

Table 41 Descriptive statistics on the derived time to PFS event, based on full analysis set of the PANORAMA-1 trial

Time to PFS event	Characteristic	Patients
PANO/BTZ/DEX, N = 387	No. of events – n (%)	207 (52.7%)
	No. of censored – n (%)	180 (47.3%)
BTZ/DEX, all patients, N = 381	No. of events – n (%)	260 (68;2%)
	No. of censored – n (%)	121 (31.8%)
BTZ/DEX, responders, N = 167	No. of events – n (%)	129 (77.2%)
	No. of censored – n (%)	38 (22.8%)

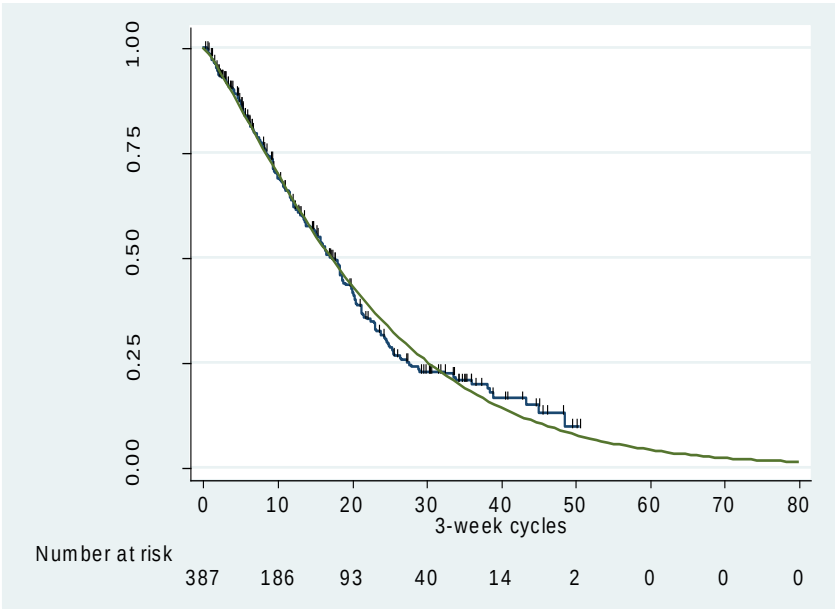
BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; PFS, progression-free survival.

'Event' corresponds to a patient who progressed or died; 'censored' corresponds to a patient who has not progressed or died at the date of the analysis cut-off, or a patient who receives any further anti-cancer therapy.

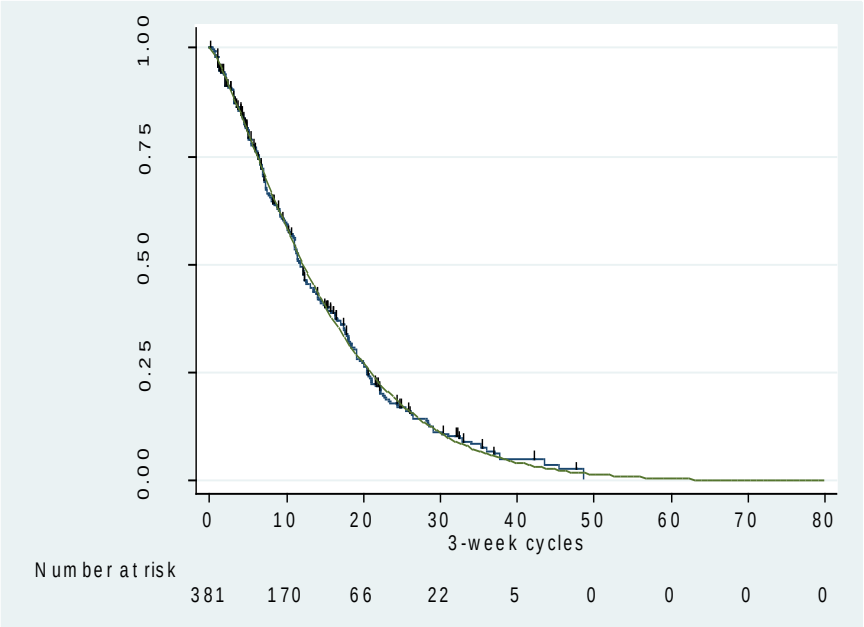
Based on the AIC and BIC statistics, clinical plausibility as well as visual assessment, the Weibull distribution was judged to provide the best model for all three curves (Figure 38). Table 42 summarises the AIC and BIC values calculated for the various survival models.

Figure 38 Kaplan–Meier curve and fitted Weibull model for PFS: full analysis set from PANORAMA-1 trial, a) PANO/BTZ/DEX, b) BTZ/DEX all patients, c) BTZ/DEX responders

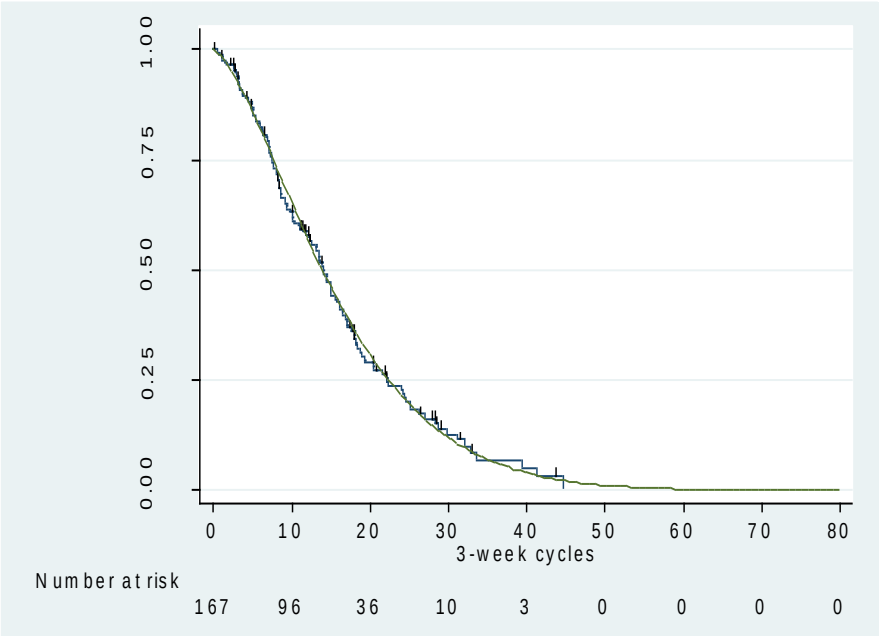
a) PANO/BTZ/DEX



b) BTZ/DEX all patients



c) BTZ/DEX responders



BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; PFS, progression-free survival.

Table 42 AIC and BIC statistics for the PFS models: full analysis set from PANORAMA-1 trial

	PANO/BTZ/DEX		BTZ/DEX, all patients		BTZ/DEX, responders	
Model	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	787.2122	791.1707	858.2095	862.1523	406.1852	409.3032
Weibull	***777.0563***	***784.9731***	***838.1121***	***845.9977***	***384.0772***	***390.313***
Lognormal	786.3762	794.2931	862.8457	870.7313	398.547	404.783
Loglogistic	778.1812	786.0981	854.3053	862.1909	391.6069	397.8429
Gompertz	784.6977	792.6145	846.6131	854.4987	391.416	397.652

The best fitting model selected for the base case analysis is shown in bold

AIC, Akaike information criterion; BIC, Bayesian information criterion; BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; PFS, progression-free survival.

Risk of progression and risk of death

The risk of experiencing a PFS event (ie either progression or death) in a given cycle was estimated using patient level data of the PANORAMA-1 trial (as described above). In a second step, the proportion of patients who progressed relative to those who had a PFS event was estimated for each cycle by a logistic regression. For the PANO/BTZ/DEX group a total of 207 patients were included in the analysis and of these, 184 experienced progression. For the BTZ/DEX overall population a total of 260 patients were included in the analysis and of these, 246 experienced progression; for the BTZ/DEX responder population, 129 patients were included in the analysis and of these 126 experienced progression. Of the three models explored (see section 5.3.1 for details), the model with the log of the cycle provided the best fit for the PANO/BTZ/DEX group and BTZ/DEX responders, whereas the model with cycle as a continuous variable provided the best fit for the BTZ/DEX overall population (see Table 43 and Figure 39).

Table 43 AIC and BIC statistics for the logistic regression models for risk of progression: full analysis set from PANORAMA-1 trial

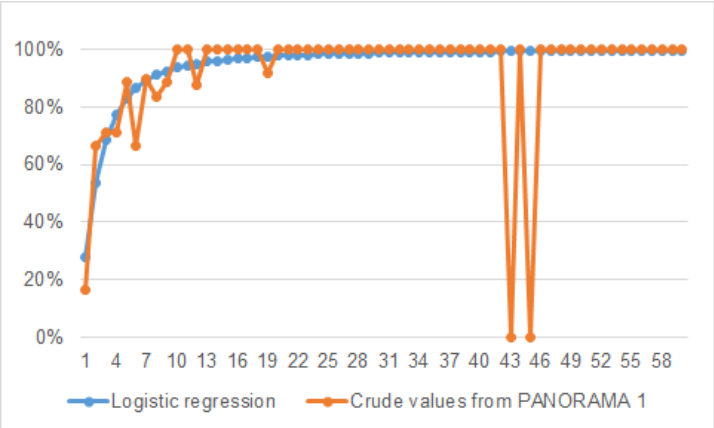
	PANO/BTZ/DEX		BTZ/DEX all patients		BTZ/DEX, responders	
Model	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Cycle	108.9222	115.5877	***90.78458***	***97.90594***	24.44292	30.16254
Cycle and cycle squared	110.2257	120.2238	92.7751	103.4571	26.25872	34.83815
Log-cycle	***107.8745***	***114.54***	91.17259	98.29396	***23.24282***	***28.96244***

The best fitting model selected for the base case analysis is shown in bold

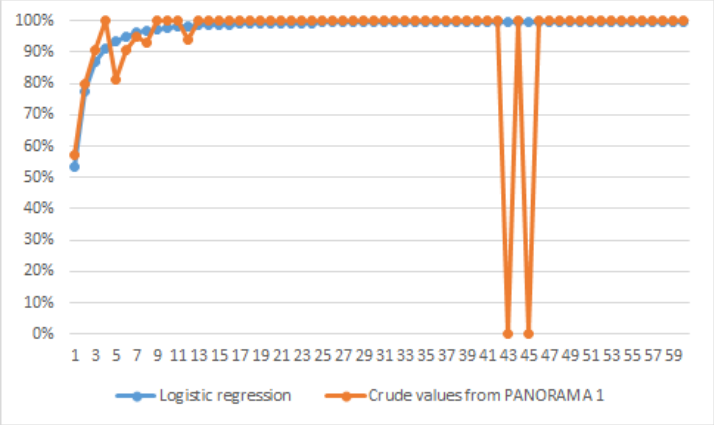
AIC, Akaike information criterion; BIC, Bayesian information criterion; BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

Figure 39 Proportion of patients experiencing progression and fitted regression model: full analysis set from the PANORAMA-1 trial, a) PANO/BTZ/DEX, b) BTZ/DEX all patients, c) BTZ/DEX responders

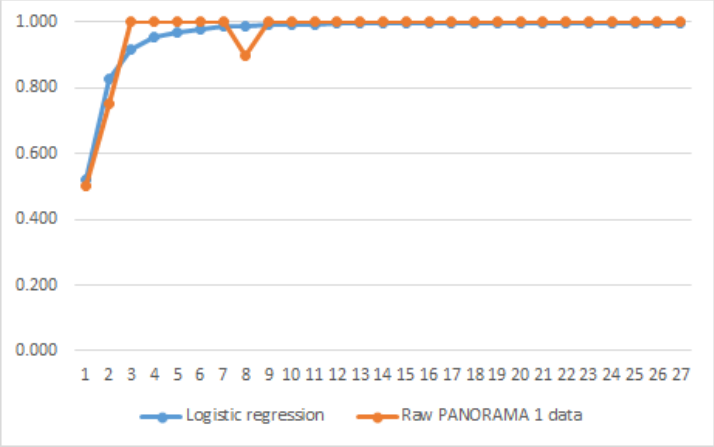
a) PANO/BTZ/DEX



b) BTZ/DEX all patients



c) BTZ/DEX responders



BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

Risk of treatment discontinuation

As described in section 5.2 in the model the pre-progression period is divided into on-treatment and off-treatment intervals. The risk of treatment discontinuation in a given 3-weekly cycle – to determine the number of patients who are on- and off-treatment – was estimated using patient-level data from PANORAMA-1 trial. In particular, treatment discontinuation data for the safety analysis set from PANORAMA-1 (ie patients who received at least one dose of study treatment; PANO/BTZ/DEX, n = 381; BTZ/DEX, n = 377; BTZ/DEX responders, n = 168) were utilized using survival analyses methods. The length of treatment exposure for a patient was considered the time to treatment discontinuation. (All patients discontinued treatment; thus no patient was censored.) The median treatment duration was 5.0 months (7.2 model cycles) for PANO/BTZ/DEX, 6.1 months (8.9 model cycles) for BTZ/DEX and 7.8 months (11.3 cycles) for BTZ/DEX responders.

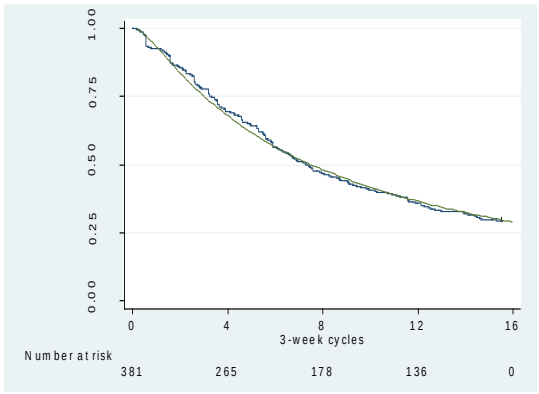
Contrary to the PANORAMA-1 trial protocol and the anticipated licence, some patients in the PANORAMA-1 trial had a documented treatment duration of greater than 48 weeks. In order to accurately capture the efficacy related cost of the treatment as per the clinical trial, these patients were not censored in the model. However, the proportions of patients continuing beyond cycle 20 are very low (proportion of patients receiving treatment in cycle 20: PANO/BTZ/DEX, 1.3%; BTZ/DEX responders, 0.8%[10]).

Five distributions (exponential, Weibull, log-logistic, log-normal, Gompertz) were fitted on the individual patient-level data to smooth the time to treatment discontinuation curves and to derive the transition probabilities. Curves were smoothed until 48 weeks, at which point the proportion of patients on treatment dropped sharply (see Figure 40 below). Beyond 48 weeks of treatment duration, treatment discontinuation rates were not smoothed. Based on the AIC and BIC statistics as well as visual assessment, the log-logistic distribution was judged to provide the best model for discontinuation while on PANO/BTZ/DEX and BTZ/DEX all patients and the exponential for the BTZ/DEX responders and were selected for the base case (see Figure 40 and Table 44). No extrapolation of the curves (and hence the transition probabilities) was needed since all patients discontinued the treatment. .

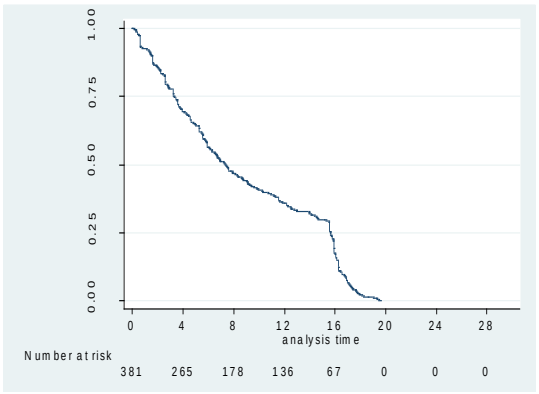
[10] Proportion of patients continuing with PANO/BTZ/DEX beyond cycle 16: cycle 17, 15.5%; cycle 18, 5.8%; cycle 19, 2.1%; cycle 20, 1.3%. Proportion of patients continuing with PBO/BTZ/DEX beyond cycle 16: cycle 17, 12.2%; cycle 18, 2.39%; cycle 19, 0.8%; cycle 20, 0.8%; cycle 21, 0.53%; cycle 22, 0.27%

Figure 40 Kaplan–Meier curve and fitted log-logistic model (a and b) or exponential model (for c) for the proportion of patients without treatment discontinuation: full safety set from PANORAMA-1 trial, a) PANO/BTZ/DEX, b) BTZ/DEX all patients, c) BTZ/DEX responders

a) PANO/BTZ/DEX

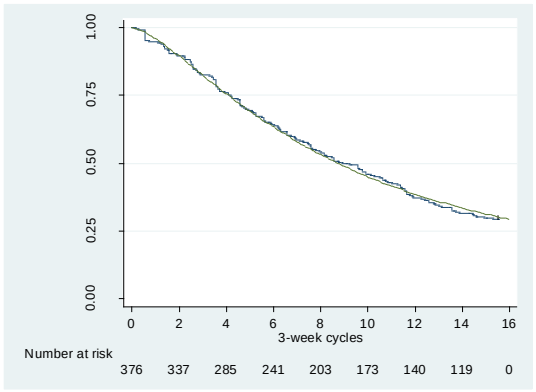


Kaplan–Meier and fitted curve (until cycle 16)

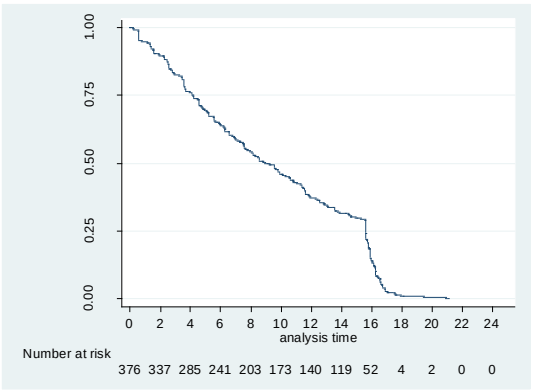


Complete Kaplan–Meier curve

b) BTZ/DEX all patients,

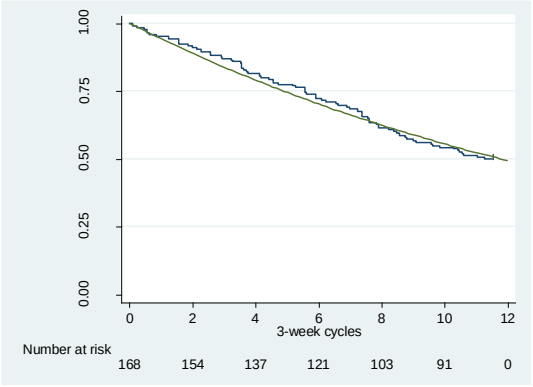


Kaplan–Meier and fitted curve (until cycle 16)

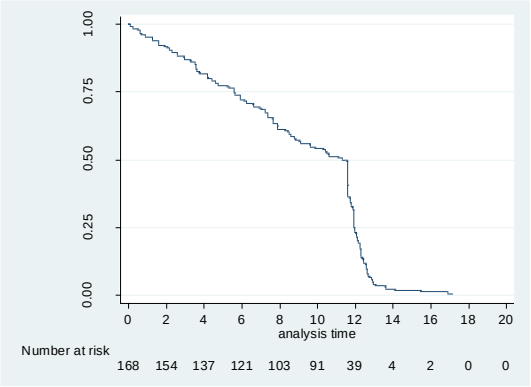


Complete Kaplan–Meier curve

c) BTZ/DEX responders



Kaplan–Meier and fitted curve (until cycle 16)



Complete Kaplan–Meier curve

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

Table 44 AIC and BIC statistics for the treatment discontinuation models: full safety set from PANORAMA-1 trial

	PANO/BTZ/DEX		BTZ/DEX all patients		BTZ/DEX responders	
Model	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	1143.781	1147.724	1061.493	1065.423	***412.3921***	***415.5161***
Weibull	1145.723	1153.608	1058.06	1065.919	413.1801	419.428
Lognormal	1137.326	1145.212	1066.241	1074.101	421.3705	427.6184
Loglogistic	***1135.511***	***1143.396***	***1057.649***	***1065.508***	414.4789	420.7268
Gompertz	1142.23	1150.116	1061.738	1069.598	413.2445	419.4924

The best fitting model selected for the base case analysis is shown in bold

AIC, Akaike information criterion; BIC, Bayesian information criterion; BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

Probability of progression and death in patients who discontinued treatment during cycle 1 to 4 (BTZ/DEX)

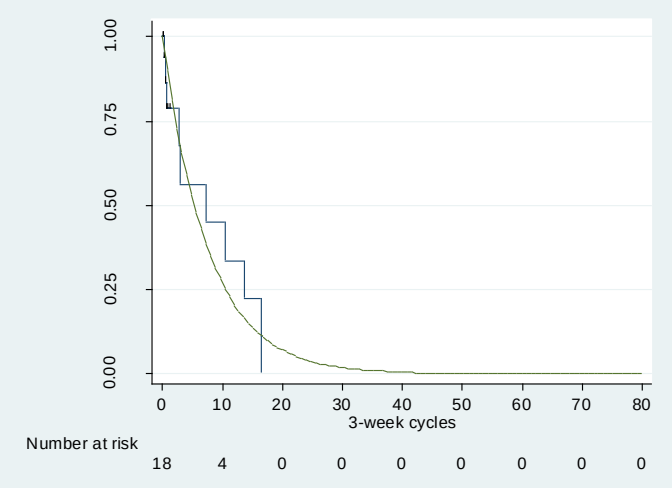
Patients who are off treatment at the end of cycle 4 because they discontinued treatment before this time point but did not experience progression afterwards until the end of cycle 4 remain off-treatment, but are subject to progression (in which case they initiate LEN/DEX treatment) and death. In the model these patients are treated separately from cycle 5 onwards.

Of 18 patients in the PANORAMA-1 population who discontinued treatment during cycles 1 to 4 and did not experience progression until the end of cycle 4, ten patients experienced progression after cycle 5 and five died[11]. Figure 41 shows the Kaplan–Meier estimates of TTP and OS in these patients, together with the estimated exponential survival curves. The exponential model was considered to provide a sufficiently good fit to the data for TTP and OS based on visual inspection.

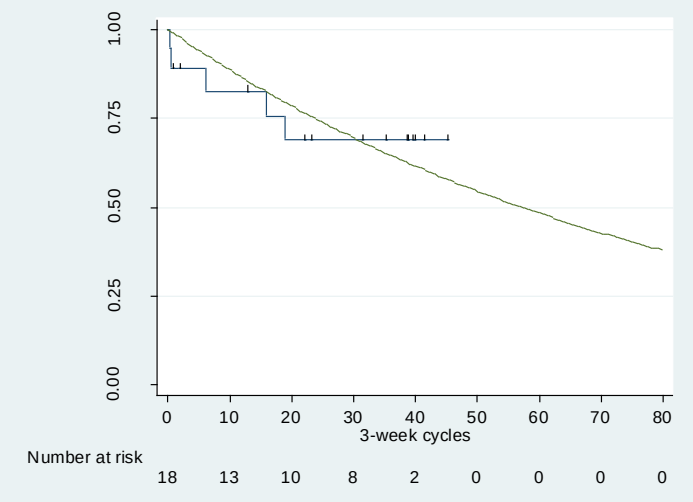
[11] Instead of pre-progression death data, overall survival data was used for these patients because only 2 patients died before / at progression, which prevented estimating a meaningful survival model. The impact of this parameter on the model results was assessed in a deterministic sensitivity analysis.

Figure 41 Kaplan–Meier plot and fitted exponential model for a) time to progression and b) overall survival in patients who discontinued BTZ/DEX before cycle 4 but did not experience progression until after cycle 4: full PANORAMA-1 population

a) TTP



b) OS



BTZ, bortezomib; DEX, dexamethasone; OS, overall survival; TTP, time to progression.

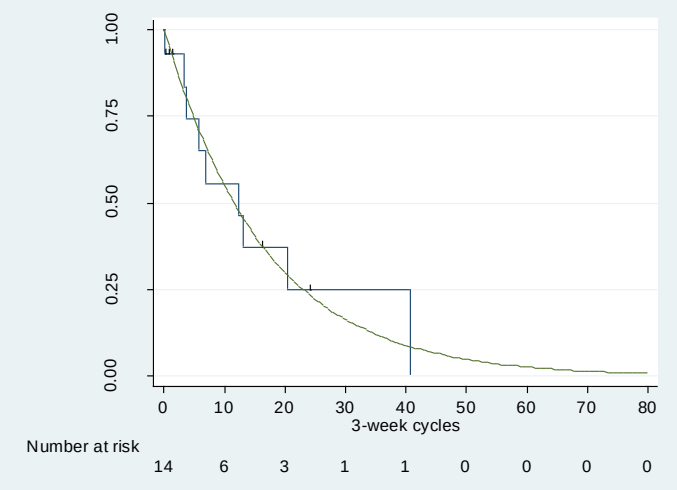
Probability of progression and death in patients who discontinued treatment during cycle 5 to 8

Patients who are off-treatment at the end of cycle 8 because they discontinued treatment between cycle 5 and 8 but did not experience progression during this period remain off-treatment, but are subject to progression and death. In the model these patients are treated separately from cycle 9 onwards.

Of 14 patients in the PANORAMA-1, nine patients experienced progression after cycle 9 and seven died[12]. Figure 41 shows the Kaplan–Meier estimates of TTP and OS in these patients, together with the estimated exponential survival curves. The exponential model was considered to provide a sufficiently good fit to the data for TTP and OS based on visual inspection.

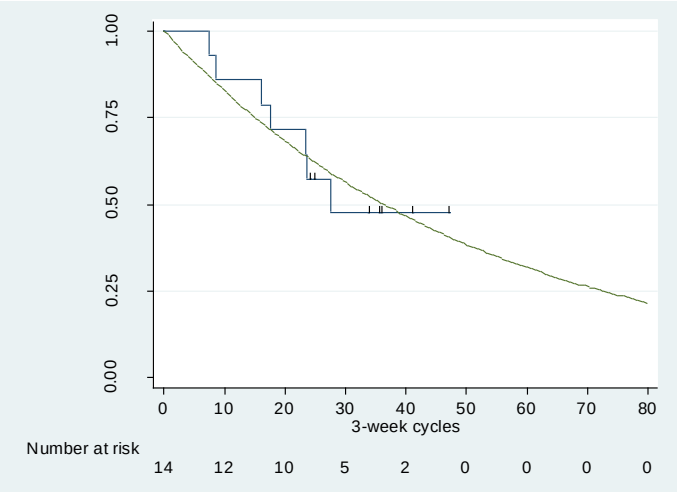
Figure 42 Kaplan–Meier plot and fitted exponential model for a) time to progression and b) overall survival in patients who discontinued BTZ/DEX during cycle 5 to 8 but did not experience progression during this period: full PANORAMA-1 population

a) TTP



b) OS

[12] Instead of pre-progression death data, overall survival data was used for these patients because no patient died before / at progression, which prevented estimating a meaningful survival model. The impact of this parameter on the model results was assessed in a deterministic sensitivity analysis.



BTZ, bortezomib; DEX, dexamethasone; OS, overall survival; TTP, time to progression.

Probability of response to BTZ/DEX

In order to correspond to current UK clinical practice as recommended in TA129[88] the following additional considerations were included for the BTZ/DEX arm.

Treatment after cycle 4

Patients who are still on BTZ/DEX after four cycles (ie did not experience progression or did not discontinue treatment due to reasons other than progression), are assessed for response to treatment. Those who achieved at least a PR continue on BTZ/DEX whereas those who did not achieve a PR or better before this time point switch to LEN/DEX treatment at the beginning of cycle 5. Time to response analysis was employed to determine the proportion of patients with a response (≥ PR) achieved after a maximum of four cycles of treatment. Time to response was a secondary outcome of the PANORAMA-1 trial. Table 45 provides descriptive statistics regarding the derived time to response dataset. The Kaplan–Meier estimates indicated that the probability of achieving a response by the end of cycle 4 was 55.12% (95% CI 39.45% to 50.15%, standard error: 0.0274, Figure 43).

It is worth noting that 55.12% denotes the probability that a patient achieves response by the end of cycle 4. Patients who achieve response during the first four cycles may also discontinue treatment (or perhaps progress) before the end of cycle 4. Thus, 55.12% should not be confused with the proportion of patients that are on treatment and have response at the end of cycle 4.

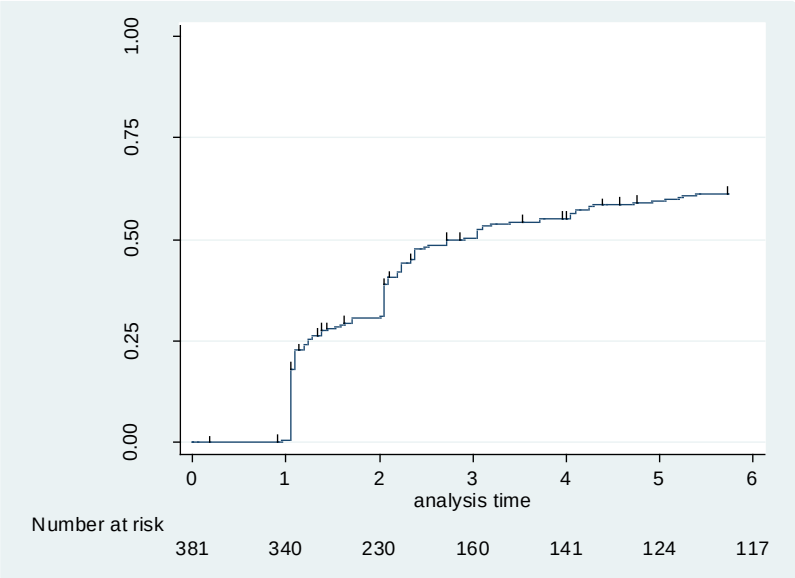
Table 45 Descriptive statistics on the derived time to response dataset

Variable	**Characteristic**	**Full PANORAMA-1 population** **N = 381**

Time to response	No. of events – n (%)	208 (54.6%)
	No. of censored – n (%)	173 (45.4%)

Event corresponds to a patient who achieved at least a PR; censored corresponds to a patient who was censored for time to response.

Figure 43 Kaplan–Meier estimates of the proportion of patients achieving a partial response or better on BTZ/DEX



BTZ, bortezomib; DEX, dexamethasone

Treatment after cycle 8

Most (90%) patients who remain on BTZ/DEX until the end of cycle 8, then stop BTZ/DEX, as per the bortezomib label and remain off-treatment until disease progression if they have at least a PR, or initiate therapy with LEN/DEX if they do not have a PR. A minority of the patients (10%) completing eight cycles of BTZ/DEX are allowed to continue on BTZ/DEX until progression or discontinuation due to other reasons up to cycle 16, as per the PANORAMA-1 protocol. (It is worth noting that the efficacy data presented for the control arm is based on the PANORAMA-1 trial that did not require patients to discontinue therapy for either of the above conditions).

As no real-world evidence is available to inform the model on the proportions of patients at this decision point at cycle 8, M-protein level data from the PANORAMA-1 trial was used. A ≥50% reduction in M-protein level versus baseline was used as a proxy for at least a PR. The proportion of patients having at least a PR was 59.5% among patients who had valid M-protein measurement at the end of cycle 8. Expert opinion suggests that no treatment is considered as an option if a patient presents with at least a PR whereas a new treatment is initiated if the response is less than a PR. Therefore in the model it was assumed that after

completing cycle 8, of those who are still on treatment at that time, 10% continue on BTZ/DEX, 49.5% stop treatment, and 40.5% switch to LEN/DEX.

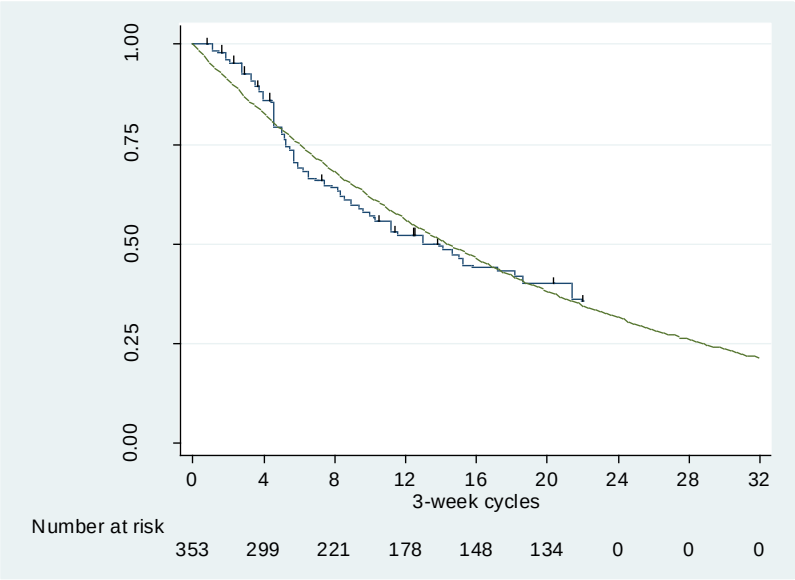
5.3.3 Clinical input parameters for LEN/DEX and LLoT

The risk of progression on LEN/DEX and the risk of post-progression death was assumed to be the same for both treatment groups (ie after PANO/BTZ/DEX and after BTZ/DEX) because no statistical difference between the treatment arms was established for post-progression death (see Appendix 16 for details).

Risk of progression on LEN/DEX

Data for progression in patients receiving subsequent antineoplastic treatments after PANO/BTZ/DEX or BTZ/DEX was not collected in the PANORAMA-1 trial. Instead, the risk of progression or death on LEN/DEX treatment (or leaving LEN/DEX health state) was estimated using published data for PFS from the pooled MM-009 and MM-010 studies.[93] In particular, the reported median PFS estimate was utilized to derive the 3-weekly hazard (and subsequently the 3-weekly probability) assuming an exponential distribution of individual progression times[13]. Based on visual inspection of the Kaplan–Meier plot and the exponential curve, the exponential model was considered to provide a sufficiently good fit to the data (Figure 44). Other curves were not tested to avoid overcomplicating the model.

Figure 44 Kaplan–Meier estimate and fitted exponential curve for time to progression for LEN/DEX



DEX, dexamethasone; LEN, lenalidomide.

[13] 3-weekly hazard of progression (λ) =3 × ln(2) / median time to progression in weeks. 3-weekly probability = 1 – exp(-λ).

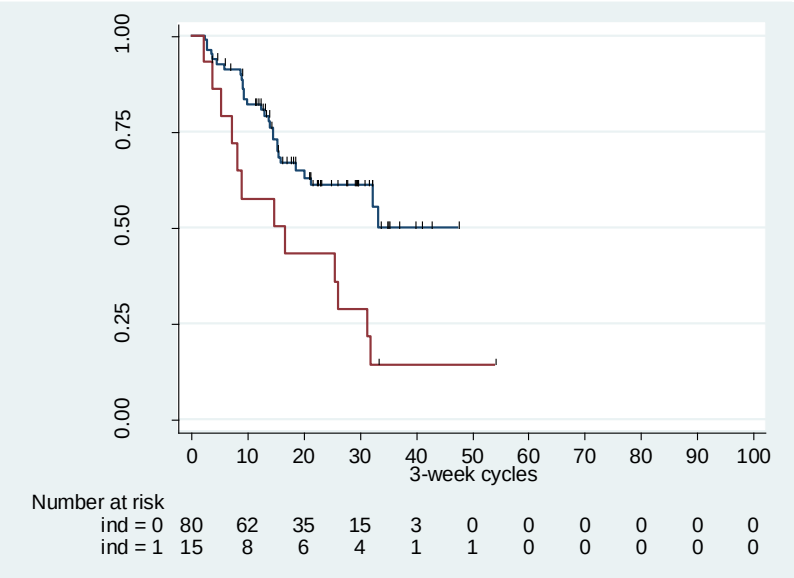
Risk of post-progression death

Transition probabilities for the risk of death in patients when receiving post-progression treatments (ie LEN/DEX and subsequent LLoT) were derived from patient-level post-progression OS data from PANORAMA-1 for patients who received LEN/DEX as subsequent antineoplastic treatment after PANO/BTZ/DEX or BTZ/DEX. This served the purpose of relying on own trial data as long as available. Exposure time was considered to be the time between initiation of LEN/DEX and last follow-up for survival.

To take into account the heterogeneity of the selected LEN/DEX patient population in terms of the risk of death, patients were stratified according to whether they experienced progression within the first four cycles (n = 15) or after the fourth cycle of therapy (n = 80). The cut-off point at cycle 4 was selected partly to mirror the time of the response assessment in the PAS for BTZ/DEX and partly as a result of exploratory analyses regarding an optimal cut-off point to define any distinct groups based on OS. It was revealed that patients who experience progression early have a higher risk of death than those who experience progression later, and a log-rank test indicated that the difference in OS between these two patient groups was statistically significant (p = 0.0045, see Figure 45). Other risk stratification strategies were also explored but did not identify any further subgroups with statistically significant differences in post-progression survival (see Appendix 16 for details). Table 46 provides descriptive statistics for the two derived OS datasets for patients receiving LEN/DEX as post-progression treatment after PANO/BTZ/DEX or BTZ/DEX.

To keep the model parsimonious, the exponential model was fitted on the individual patient level data of both the above groups, ie early and late progressors. Based on visual inspection of Kaplan–Meier and fitted curves, the exponential models were considered to provide a sufficiently good fit to the data (Figure 46).

Figure 45 Overall survival for patients who received LEN/DEX on progression in PANORAMA-1, stratified according to whether patients experienced progression during cycle 1 to 4 or later



Progression during cycle 1 to 4: ind = 1; progression later than cycle 4: ind = 0

Log-rank test: chi^2 = 8.05; p = 0.0045

DEX, dexamethasone; LEN, lenalidomide.

Table 46 Descriptive statistics on the derived overall survival datasets for patients receiving LEN/DEX as post-progression treatment

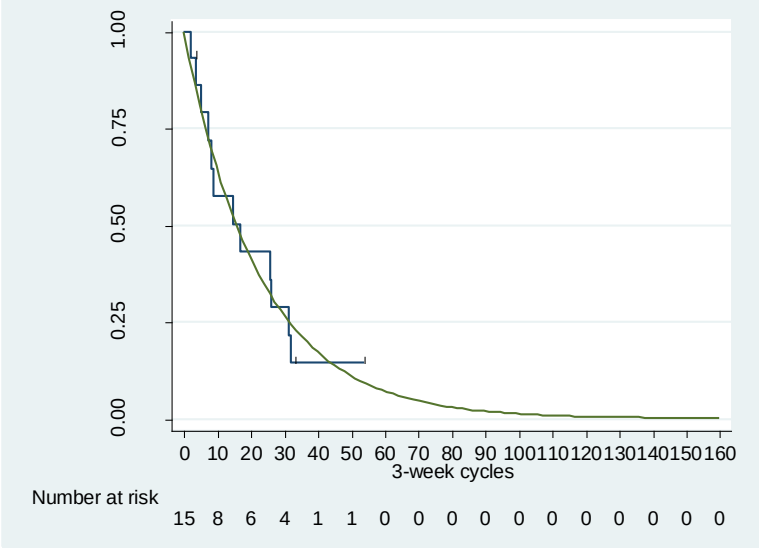
Variable	Characteristic	Patients who received LEN/DEX as post-progression treatment
Overall survival (progression during 1 to 4 cycles)	No. of events – n (%)	12 (80%)
	No. of censored – n (%)	3 (20%)
Overall survival (progression after cycle 4)	No. of events – n (%)	29 (36.3%)
	No. of censored – n (%)	51 (63.8%)

Event corresponds to a patient who died during follow-up for survival; censored corresponds to a patient who did not die during follow-up for survival.

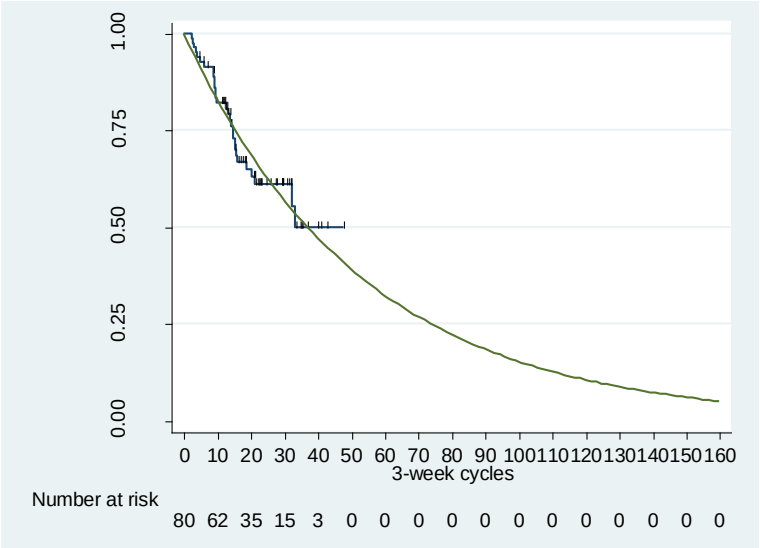
DEX, dexamethasone; LEN, lenalidomide.

Figure 46 Kaplan–Meier curve and fitted exponential model of overall survival for patients receiving LEN/DEX as post-progression treatment in the PANORAMA-1 trial and progressed a) during cycle 1 to 4 and b) after cycle 4

a)



b)



DEX, dexamethasone; LEN, lenalidomide.

5.4 Measurement and valuation of health effects

Multiple myeloma is an incurable disease; patients diagnosed with rrMM often suffer with pronounced symptoms and thus a decreased HRQL, see section 3.2 for details.

5.4.1 Health-related quality-of-life data from clinical trials

In the PANORAMA-1 trial, the EORTC QLQ-C30 questionnaire and the MM-specific module, EORTC-MY20, were used to provide patient-reported outcome measures of HRQL, disease symptoms and treatment-related adverse events. The EORTC QLQ-C30 and EORTC QLQ-MY20 are frequently employed in clinical trials of patients with MM and are recognised as reliable and valid measures.[133] The EORTC QLQ-C30 includes five functional dimensions (physical, role, emotional, cognitive, and social), three symptom items (fatigue, nausea/vomiting, and pain), six single items (dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea and financial impact) and a global health and quality-of-life scale (GHS). The EORTC QLQ-MY20 was used in conjunction with the EORTC QLQ-C30 and provides an additional 20 items grouped into four domains: symptoms, treatment adverse events, social support and future perspective. The recall period for both measures is the past week. For both questionnaires, scores are averaged and transformed linearly to a score ranging from 0 to 100 with high scores being indicative of better functioning for the QLQ-C30 functional domains and GHS/quality of life and better outcomes for QLQ-MY20 Future perspective and Body Image, while for the QLQ-C30 symptom scores and single items, together with the QLQ-MY20 Disease Symptoms and Side Effects of Treatment domains, low scores are indicative of fewer symptoms or side effects.

The EORTC QLQ-C30 and EORTC QLQ-MY20 were administered at screening and before study drug treatment on cycle 1 day 1 (C1D1) and every six weeks thereafter (ie C3D1, C5D1, C7D1, C9D1, C10D1, C11D1, C12D1), and during the study completion visit, but assessments were not performed in patients who discontinued treatment early (eg due to adverse event or disease progression) and were not continued during follow-up after completion of treatment (whether in remission or on disease progression). The measures were administered sequentially at the beginning of the study visit prior to any interaction with the study physician (including any tests, treatment or receipt of results from any tests) to avoid biasing the patient.

However, the EORTC QLQ-C30 and EORTC QLQ-MY20 cannot be used directly in economic evaluation as they do not provide preference based utilities as are required for use in the economic model. A mapping approach was therefore employed.

5.4.2 Mapping

As the EORTC QLQ-C30 and EORTC QLQ-MY20 cannot be used directly in economic evaluation, a targeted literature search was performed to identify appropriate mapping algorithms that could be used to map the EORTC patient reported outcome measures to EQ-5D utility measures. A search was conducted in PubMed and in the University of Oxford Health Economics Research Centre (HERC) mapping database.

Four references were identified in PubMed or the HERC mapping database that described mapping algorithms from the EORTC QLQ-C30 and/or the EORTC QLQ-MY20 to the EQ-5D based on data for patients with MM.[134-137]

- Versteegh et al., 2012
- Kharroubi et al., 2014
- Longworth et al., 2014
- Proskorovsky et al., 2014.

Studies reported by Versteegh et al[134] and by Kharroubi et al[136] both employed data for patients with newly-diagnosed MM [enrolled in the HOVON trial (n = 137) and the Myeloma IX trial (n = 1244), respectively], and the study reported by Longworth et al.[137] employed pooled data for patients (n = 771) with newly-diagnosed MM (from the VISTA trial), breast cancer or lung cancer. In contrast, the fourth study reported by Proskorovsky et al.[135] was based on data for patients with MM (presenting for routine care visits at five UK and six German sites) of whom approximately 50% had received more than one prior treatment and therefore corresponded more closely to the patient population of the PANORAMA-1 trial (ie patients having received 1 to 3 prior treatments). Table 47 summarises the baseline demographics and disease characteristics for patients in PANORAMA-1 and the cohort used in the mapping study of Proskorovsky et al. The mapping algorithm described by Proskorovsky et al[135] was therefore selected as being most appropriate for deriving utility values from data from the PANORAMA-1 trial.

Table 47 Summary of baseline demographics and disease characteristics for patients in PANORAMA-1 and involved in the Proskorovsky et al. mapping study.

Variable	**Proskorovsky et al. (n = 154)**	**PANORAMA-1 trial (n = 768)**
Male – n (%)	97 (63%)	407 (52.9%)
Age – mean (SD)	66.4 (10.0)	62.1 (9.4)
Nationality British German Other	 73 (47%) 56 (36%) 25 (16%)	 30 (3.9%) 63 (8.2%) 675 (87.9%)
Duration of MM (years) – mean (SD)	3.7 (3.7)	4.6 (8.7)
Previous ASCT	18 (12%)	440 (57.2%)

ASCT, autologous stem cell transplantation; MM, multiple myeloma; SD, standard deviation

San Miguel et al 2014;[9] Proskorovsky et al 2014[135]

HRQL scores for the cohort of patients involved in the Proskorovsky et al. study are summarised in Table 48 (see section, 5.4.1 for interpretation of the scores). The mean (± standard deviation [SD]) EQ-5D utility value was 0.7 ± 0.3 and the minimum and maximum observed values were −0.13 and 1.0, respectively. The mean QLQ-C30 GHS/quality of life score was 60.1 ± 25.5. Mean scores for CF and EF were approximately 80, while those for RF, SF and PF were between 60 and 70. Mean pain and fatigue scores were 32.3 and 38.6, respectively, while scores for insomnia and dyspnoea were lower (25.1 and 21.9, respectively), indicative of less severe symptoms, and diarrhoea and nausea/vomiting scales had the lowest mean scores (< 10).

For the QLQ-MY20 instrument, the score for Body Image scores was high (77.9), indicative of a relatively good outcome, whereas the score for Future Perspective was lower (59.9), indicative of MM affecting this aspect of a patient's life. Scores for Disease Symptoms (23.3) and Treatment Side Effects (19.5) were consistent with the symptom scales from the QLQ-C30.

Table 48 Summary of HRQL scores used in the mapping algorithm of Proskorovsky et al

HRQL domain	Mean ± SD (IQR)
EQ-5D	
EQ-5D	0.7 ± 0.3 (0.62 to 1.00)
EORTC QLQ-C30	
GHS/quality of life	60.1 ± 25.5 (41.7 to 83.3)
Cognitive Functioning	81.4 ± 22.9 (66.7 to 100.0)
Emotional Functioning	78.1 ± 24.6 (66.7 to 100.0)
Role Functioning	62.9 ± 34.6 (33.3 to 100)
Social Functioning	63.9 ± 32.9 (33.3 to 100)
Fatigue	38.6 ± 29.8 (11.1 to 66.7)
Nausea/vomiting	5.2 ± 11.8 (0 to 0)
Pain	32.3 ± 33.4 (0 to 66.7)
Dyspnoea	21.9 ± 30.6 (0.0 to 33.3)
Insomnia	25.1 ± 29.8 (0.0 to 33.3)
Appetite loss	15.4 ± 27.0 (0.0 to 33.3)
Constipation	17.7 ± 28.6 (0.0 to 33.3)
Diarrhoea	8.4 ± 21.7 (0.0 to 0.0)
Financial difficulties	18.4 ± 31.2 (0.0 to 33.3)
EORTC QLQ-MY20	
Disease symptoms	23.3 ± 22.3 (0.0 to 38.9)
Side-effects of treatment	19.5 ± 17.1 (7.4 to 29.6)
Future perspective	59.9 ± 28.1 (33.3 to 77.8)
Body image	77.9 ± 30.5 (66.7 to 100.0)

Proskorovsky et al 2014[135]

EORTC, European Organization for Research and Treatment of Cancer; EORTC QLQ-C30, quality of life questionnaire-core 30; EORTC QLQ-MY20, EORTC MM-specific module; EQ-5D, 5-dimension EuroQol questionnaire; GHS, Global health Status; HRQL, health-related quality of life; IQR, interquartile range; SD, standard deviation.

Proskorovsky et al. used multiple linear regression analyses to derive a mapping algorithm 1) from EORTC QLQ-C30 and QLQ-MY20 to EQ-5D utilities, and 2) from EORTC QLQ-C30 alone to EQ-5D utilities. The model selection strategy described below applied to both models. Each scale/item was tested in univariate models against utility. The first multivariate model was fitted by including scales/items that were found to have a statistically significant association with utility in univariate analysis ($p < 0.1$). The first multivariate model was then manually trimmed down by sequentially removing non-significant predictors with the highest p-value until the final model included only significant predictors (p-value for all predictors must have been < 0.1). Goodness-of-fit of the models including only the significant predictors was calculated using the adjusted R-squared measure. More details on the methodology used to derive the mapping algorithm, predictive ability, and cross-validation can be found in the publication of Proskorovsky et al.[135]

Both models had similar and good explanatory power – adjusted R-squared values of 0.703 (ie mapping QLQ-C30 and MY20 to EQ-5D) and 0.694 (ie mapping QLQ-C30 to EQ-5D) for the trimmed models. Since there was hardly any difference between the two models in terms of explanatory power, in order to use as many patients with HRQL information as possible from the PANORAMA-1 trial the more parsimonious mapping model (ie the one that mapped QLQ-C30 to EQ-5D) was selected for use. (This model required patients with complete HRQL data from the relevant domains of the QLQ-C30 questionnaire whereas the more complex model would have required patients with complete HRQL data from the relevant domains of both the QLQ-C30 and the QLQ-MY20 questionnaires.)

The mapping function that was used for the health economic model took the following form:

EQ-5D = 0.23004 + 0.00191 * GHS score + 0.00478 * PF score + 0.00136 * EF score −0.00249 * Pain score.

Patients in the PANORAMA-1 trial with complete EORTC QLQ-C30 information on these four items were selected for inclusion in the mapping. For each included patient at each measured time point the QLQ-C30 value was mapped to obtain the corresponding EQ-5D utility value using the mapping algorithm described above. No adjustment was applied in cases where mapped values were higher (or lower) than the maximum (or minimum) EQ-5D utility score. Cycle-specific and overall mean and median utility values were estimated for both treatment groups.

The cycle-specific mapped utility values were lower for PANO/BTZ/DEX than for BTZ/DEX at all time points, as expected from the differences in safety profile between the two treatments (see section 4.12). The overall mean ± SD utility values for the full PANORAMA-1 population were estimated to be 0.706 ± 0.192 for PANO/BTZ/DEX and 0.725 ± 0.197 for BTZ/DEX.

The overall mean value for the corresponding treatment group was used for the pre-progression on treatment states (ie Health State A; pre-progression: PANO/BTZ/DEX and 'pre-progression: BTZ/DEX). These were thus 0.706 and 0.725, respectively for pre-progression: PANO/BTZ/DEX and 'pre-progression: BTZ/DEX.

Acaster et al[23] report that HRQL improves when patients come off-treatment compared to when they were on-treatment (prior to stopping therapy, see section 3.2). Furthermore, when off-treatment patients do not experience the adverse events associated with active treatment. Thus utility values for the pre-progession, No treatment health state can be assumed to be higher than for the pre-progression, on-treatment health states. In PANORAMA-1, HRQL was not measured in patients who discontinued treatment (for example due to adverse events or disease progression) or after completion of treatment (see section 5.4.1). Therefore, the utility value associated with the 'pre-progression, no-treatment' health state was assumed to be equal to the mean utility value (0.762) mapped from the last HRQL assessment while still on treatment and was based on pooled data from both treatment groups.

No HRQL data from PANORAMA-1 was available for the post-progression health states. Instead, utility values published by van Agthoven et al[138] was used for the two post-progression states corresponding to Health State C (third-line therapy) and D (LLoT). Following previous health economic models submitted to NICE[52,87] 0.64 was adopted for both post-progression health states. The utility value associated with death was assumed to be zero. Table 49 summarises the utility values used in the model.

Table 49 Utility values applied in the model

Health state	Utility (SD) n = 4172[a]
A: Pre-progression, PANO/BTZ/DEX	0.706 (0.192)
A: Pre-progression, BTZ/DEX	0.725 (0.197)
B: Pre-progression, No treatment	0.762 (0.166)
C and D: Post-progression, LEN/DEX and Post-progression, LLoT	0.64 (0.129)[b]
Dead	0

[a] Number of HRQL measurements, 2031 and 2141 on PANO/BTZ/DEX and BTZ/DEX arms, respectively; [b]Standard error, assumed to be 20% of the mean value.

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; LLoT, last line of treatment; PANO, panobinostat; SD, standard deviation.

5.4.3 Health-related quality-of-life studies

A systematic review was performed in August 2013 to identify evidence for the humanistic burden of disease in patients with rrMM or MM. Updates to the review were performed on 24 April 2014 and 3 to 9 December 2014. The search aimed to identify studies reporting on the HRQL in patients with MM or rrMM and the impact of treatments for rrMM on HRQL. Specific inclusion and exclusion criteria were utilized to identify relevant references. Two analysts independently screened each reference for inclusion based on title and abstract. A third researcher resolved any differences between results. All publications that met entry criteria for the review were obtained as full articles and reassessed against the review criteria. Data from the selected studies were subsequently used to populate predefined summary tables. All data were fully checked by the third analyst. Further details of the methodology for the reviews are provided in Appendix 13.

To be included in this systematic review, references had to meet the inclusion criteria (and none of the exclusion criteria) detailed in Table 50.

Table 50 Eligibility criteria used in the screening

Variable	Inclusion Criteria	Exclusion Criteria
Populations	MM with HRQL assessment during specific treatment for rrMM MM with HRQL relating to stage of disease/treatment MM and reporting on carer HRQL or patient unmet needs MM and reporting on patient preferences	HRQL assessment during or after specific first-line therapy or during or after ASCT or where information for rrMM cannot be clearly separated from other data.
Interventions	Any treatments used for rrMM No specific intervention	Specific first-line therapies or ASCT
Outcomes	HRQL measures obtained using EORTC QLQ-C30, QLQ-MY20, QLQ-MY24, EQ-5D, FACIT-Fatigue, FACT/GOG-Ntx Questionnaires relating to unmet needs of patients and carers, burden of living with MM Mapping studies or studies deriving preference-based measures for MM	
Study design	Any	
Publication type	Published from March 2013 to April 2014	Published before March 2013 Editorial Review Letter Reference included in original systematic review
Language restrictions	English	Non-English languages

ASCT, autologous stem cell transplantation; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, 5-dimension EuroQoL questionnaire; FACIT-Fatigue, The Functional Assessment of Chronic Illness Therapy; FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity; HRQL, health-related quality of life; MM, multiple myeloma; QLQ, Quality of Life Questionnaire; rr, relapsed/refractory.

Six studies were identified which reported on HRQL associated with MM or rrMM (Table 51). Only one of the studies reported utility values; specifically Acaster et al[23] reported utilities values for stages of treatment: first-line treatment, 0.63; first treatment-free interval, 0.72; second-line treatment, 0.67; and later-stage disease, 0.63. The other studies report HRQL as assessed using non-preference-based instruments. Petrucci et al,[65] in agreement with Acaster et al, reported an improved HRQL in patients in remission or who were asymptomatic compared with those receiving treatment, while a further study reported on the decrease in HRQL according to symptom severity.[67]

A further five studies were identified which reported on the impact of specific treatments on HRQL in patients with rrMM (see Appendix 13). None of these studies used preference-based

instruments. One study reported improvements in HRQL scores for responding patients and decreases in HRQL for patients in progressive disease,[139] and thus provide further support for use of a higher utility value for the progression-free no treatment health state.

Table 51 Studies reporting HRQL according to stage of disease, treatment or symptoms

Reference/study (by treatment)	Study design and objective	Cohort characteristics	Instruments	Results	Conclusions
Acaster, et al; 2013[23] (NR)	Cross-sectional postal survey comparing HRQL scores according to stage of disease	N = 370 Mean age:64 years (37–82) Stage of disease: First-line, n = 12; First TFI, n = 177; Second-line, n = 59; Later stages, n = 122	EORTC QLQ-C30 EORTC QLQ-MY20 EQ-5D Assessed at a single time point	QLQ-C30 and QLQ-MY20: Mean scores for most domains higher in patients in first TFI versus other phases Length of the first TFI positively associated with HRQL EQ-5D utility values: First-line therapy, 0.63; First TFI, 0.72; Second-line therapy, 0.67; Later-stage disease, 0.63	Provided utility and HRQL values for rrMM according to stage of treatment
Petrucci, et al; 2009[65] (12 months) [abstract] Italy	Cross-sectional retrospective survey of HRQL according to stage of disease and treatment	N = 199 Median age: NR Stage of disease: asymptomatic (16%); symptomatic, receiving ABMT (12%); symptomatic, receiving drugs (45%); plateau/remission	EORTC QLQ-C30 EORTC QLQ-MY24 Assessed at a single time point	QLQ-C30 GHS: Overall: 60.93 Asymptomatic: 71.05 Autotransplanted: 57.41 Receiving drugs: 49.25 Plateau/remission: 72.02	Provided HRQL scores according to stage of disease/treatment and reported that patients in remission had a similar HRQL to those with asymptomatic disease

Reference/study (by treatment)	Study design and objective	Cohort characteristics	Instruments	Results	Conclusions
		(including BSC) (27%)			
Kyriakou, et al; 2013[140] (NR) [abstract] European Multicentric study	Observational study assessing factors predictive of HRQL in patients receiving second-or third-line therapy	N = 155 Mean age: 69 years	EORTC QLQ-C30 EORTC QLQ-MY20 EORTC QLQ-CIPN20 Assessed at a single time point at initiation of second-line or third-line therapy	Multivariate linear regression identified baseline factors associated with worse HRQL: Poor ECOG performance status, prior prednisone therapy, chronic heart failure, cumulative dosage of BTZ received	Provided data on impact of baseline clinical factors on HRQL
Broek, et al; 2013 (NR)[141] [abstract] European Multicentre Observational study	Observational study assessing concordance between patient and physician ratings of HRQL in patients receiving second- or third-line therapy	N = 155 Mean age: 69 years	EORTC QLQ-C30 EORTC QLQ-MY20 EORTC QLQ-CIPN20 Assessed at a single time point at initiation of second-line or third-line therapy Comparison of patient versus physician assessments	Good concordance between patient and physician ratings for GHS and functional domains Poor concordance for scores relating to symptoms and side effects: constipation, diarrhoea, nausea and vomiting, dyspnea, insomnia, side effects; autonomic scale, motor scale and sensory scale of QLQ-MY20; financial difficulties and body image	Physicians provided reliable assessment of the impact of MM on patient functioning but underestimated the impact of symptoms and side effects

Reference/study (by treatment)	Study design and objective	Cohort characteristics	Instruments	Results	Conclusions
Jordan et al; 2014[67] [full paper]	Cross-sectional, bi-national, multicentre study. Study to quantify the effects of general symptom level, specific symptoms, and treatment-related AEs on MM patients' HRQL	N = 154 (89 from UK, 65 from Germany) Age mean (SD): 66.4 (10.0) years Four groups: Asymptomatic (17, 11%); mildly symptomatic (48, 31%), moderately symptomatic (50, 32%), and severely symptomatic (39, 25%). Currently receiving therapy: 80 (52%) BTZ, 37 (46%) LEN, 17 (21%) THAL, 15 (19%) Alkylating agents: 8 (10%) Other: 3 (4%) Prior therapy (n,	EORTC QLQ-C30 and QLQ-MY20 Administered at a single patient visit. Multiple regression analyses of data.	Overall mean scores: GHS (SD), 60.1 (25.5) Physical functioning (IQR), 68.7 (53.3–93.3) Social functioning (IQR), 63.9 (33.3–100) Future Perspectives (IQR), 59.9 (33.3−77.8) GHS according to symptom severity (asymptomatic to severe): 78.9, 71.2, 56.2, 43.2 Physical functioning: 91.0, 81.5, 66.1, 46.5 Social functioning: 87.3, 78.1, 57.3, 44.4 Future Perspective: 70.6, 69.4, 54.7, 50.1 Fatigue and Disease Symptom scores according to symptom severity (asymptomatic to severe) Fatigue: 15.7, 22.7, 46.4, 58.1 Disease Symptoms: 13.7, 14.8, 23.6, 37.7 Most commonly reported symptoms:	Moderate and severe general symptom levels, bone symptoms, depression, and mental status changes were identified as strong determinants of HRQL. Patients with severe bone pain had an additional 21-point reduction in score compared with those who had none or only mild or moderate bone pain. Depression and moderate fatigue had similar effects on GHS/QoL scores and each was associated with an 11-point reduction in score. Each additional year with MM was associated with a QoL reduction of 1 score point. Receiving any type of MM treatment within the past 30 days was also associated with a 9.5-point reduction in the GHS/QoL score Patients with severe and moderate bone pain reported on average 38- and 18-point higher Disease Symptoms scores, respectively, compared with patients with mild or no bone pain. Muscle cramps were

Reference/study (by treatment)	Study design and objective	Cohort characteristics	Instruments	Results	Conclusions
		%): None: 88 (57%) One: 49 (32%) Two: 13 (8%) ≥ Three: 4 (3%)		Fatigue : 59% Bone pain : 51% Sleepiness: 36% Hypoesthesia / paraesthesia : 33% Muscle cramps : 31% Peripheral oedema : 26% Insomnia : 25%	associated with an 11-point increase in Disease Symptoms score. Longer duration of current treatment and being male were associated with an increase in the Disease Symptoms score. Patients whose current treatment regimen contained BTZ, LEN or alkylating agents/other treatments reported, on average, an increase of ≥ 10 points in their Fatigue score compared with patients not receiving treatment. GHS and functioning domains − higher scores correspond to better HRQL Symptoms domains – higher scores correspond to worse symptoms

Reference/study (by treatment)	Study design and objective	Cohort characteristics	Instruments	Results	Conclusions
Pamuk et al., 2013[142] [abstract]	Evaluate anxiety, depression, HRQL in patients with MM and determined the association between these disorders and patients' demographic characteristics.	N = 89 54 Males; 35 females; Age, mean (SD) : 62.4 (10.1)	EORTC-QLQ-C30, EORTCQLQ-MY20, HADS	EORTC QLQ scores: Fatigue, 48.7 ± 27.3, Pain, 40.2 ± 30.3, Insomnia, 33.3 ± 35.2 Appetite loss, 32.9 ± 37.5. Function scale scores: Financial function, 23.6 ± 30.6 (lowest function scale score) Cognitive function, 80.3 ± 20.7 (highest function scale score) Patients with depression versus patients without depression had: lower global QoL scores (64.7 ± 24 versus 34 ± 22.3, p > 0.001); higher QLQ-MY20 scores (p > 0.05), and had significantly higher pain, fatigue, dyspnea and appetite loss scores (p > 0.001); and lower physical, role, social and emotional function scores (p > 0.001). Physical function score (OR: 4.48; p = 0.028) and role function score (OR:3.82; p = 0.03) positively influenced the global QoL score	Pamuk et al., 2013 [abstract]

Reference/study (by treatment)	Study design and objective	Cohort characteristics	Instruments	Results	Conclusions
				independently. Treatment side effect score of EORTC-QLQ-MY20 (OR: –2.20; p = 0.01) and the presence of depression (OR: −1.7; p = 0.007) were independent factors which negatively influenced the global QoL score.	

AE, adverse event; ABMT, autologous bone marrow transplantation; BSC, best supportive care ; BTZ, bortezomib; CIPN, chemotherapy-induced peripheral neuropathy; ECOG, Eastern Cooperative Oncology Group; EORTC-QLQ, European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire; EQ-5D, 5-dimension EuroQoL questionnaire; GHS, global health status; HADS, Hospital Anxiety and Depression Scale; HRQL, health-related quality of life; IQR, interquartile range; LEN, lenalidomide; MM, multiple myeloma; NR, not reported; OR, odds ratio; QLQ, Quality-of-Life Questionnaire; QLQ-C30, quality of life questionnaire-core 30; QLQ-MY20, EORTC MM-specific module; QoL, quality of life; rr, relapsed/refractory; SD, standard deviation; TFI, treatment-free interval; THAL, thalidomide.

The only published utility values for patients with MM are those published by van Agthoven et al 2004[138] which relate to patients receiving first-line therapy and those published by Acaster et al[23] which related to different stages of treatment. The pre-progression utility value reported by van Agthoven et al for patients receiving chemotherapy, 0.81, is higher than the values of 0.706 and 0.725 used here in the economic evaluation for health state A (for PANO/BTZ/DEX and BTZ/DEX, respectively). This is as expected given that the van Agthoven et al data relate to patients receiving first-line therapy. The utility value used in the economic model for the post-progression health state (0.64) is the value calculated by van Agthoven et al and is applied in previous rrMM NICE appraisals. Van Agthoven describes calculating this value based on taking the utility value for the general population for the relevant age group and applying a correction factor for "intentionally curative primary therapy". van Agthoven et al do not report a utility value for pre-progression off-treatment.

Acaster et al[23] reports utility values for first-line therapy (0.63), treatment free remission (0.72), second-line therapy (0.67) and later disease (0.63). These values indicate an improvement of 0.09 points associated with treatment-free remission following first-line therapy in comparison with improvements of 0.049 and 0.019 for PANO/BTZ/DEX and BTZ/DEX, respectively, used in the economic model. The smaller improvement is consistent with the lower utility values used in the model for pre-progression on treatment, which reflects the fact that patients in the model have rrMM not newly-diagnosed disease. Acaster et al report a value of 0.63 for later stage disease which is thus similar to the post-progression utility value of 0.64 used in the economic model. However Acaster et al report a value of 0.67 for second-line therapy, thus suggesting a lower HRQL during second-line therapy than was measured in PANORAMA-1 and mapped for the economic model (ie 0.706 and 0.725 for the PANO/BTZ/DEX and BTZ/DEX arms, respectively).

5.4.4 Adverse reactions

Data from PANORAMA-1 indicate that HRQL during treatment with PANO/BTZ/DEX is lower than that in patients receiving BTZ/DEX (see section 4.7.5), presumably reflecting the increased incidence of adverse events (see section 4.12). This is reflected in the model by the use of a lower utility value for the pre-progression health state associated with treatment with PANO/BTZ/DEX compared with that for BTZ/DEX (see Table 49).

5.4.5 Health-related quality-of-life data used in cost-effectiveness analysis

As demonstrated in two papers identified in a systematic review (see section 5.4.3), HRQL in patients with MM varies according to stage of treatment and response to treatment. A cross-sectional survey of patients with MM found that HRQL is highest for patients in treatment-free remission and is lower in patients receiving treatment and in patients with later stages of disease beyond second-line therapy.[23] A further study has reported an improved HRQL in patients in remission or who were asymptomatic compared with those receiving treatment,[65] and an analysis of data from a trial of bortezomib

monotherapy has revealed an improvement in certain aspects of HRQL and symptoms in patients achieving at least a PR compared with those with progressive disease.[139]

The health states in the model capture the impact of treatment, the treatment-free interval between treatments, and later lines of therapy on HRQL. HRQL is assumed to be constant within each health state, and the mean HRQL measured throughout the model corresponds to that for the pre-progression on treatment health states.

Table 52 summarises the utility values used in the model. Values for the pre-progression on-treatment health states (Health state A) and pre-progression off-treatment health state (Health state B) are derived from data from the pivotal phase 3 trial (which compared PANO/BTZ/DEX and BTZ/DEX) using a mapping algorithm, as described earlier. This approach is recommended by NICE when EQ-5D data are not available. The mapping section includes discussion of the identification of possible mapping functions that have been used to map from the EORTC QLQ-C30 or EORTC QLQ-MY20 to EQ-5D together with the rationale for the mapping function chosen for this analysis. No data from PANORAMA-1 were available to derive utility values for the post-progression health states. Instead, the utilities values published by van Agthoven et al[138] (see section 5.4.3) were used for the two post-progression states corresponding to Health State C (third-line treatment) and D (LLoT). The utility value associated with death was assumed to be zero.

Table 52 Summary of quality-of-life values for cost-effectiveness analysis: full population

State	Utility value, mean	Confidence interval, SD	Reference in submission	Justification
A: Pre-progression, PANO/BTZ/DEX	0.706	0.192	Mapping	Derived using mapping from trial data
A: Pre-progression, BTZ/DEX	0.725	0.197	Mapping	Derived using mapping from trial data
B: Pre-progression, No treatment	0.762	0.166	Mapping	Assumed to equal the mean mapped utility value measured at the last treatment cycle
C and D: Post-progression, LEN/DEX, and Post-progression, LLoT	0.64	0.128[a]	van Agthoven et al 2004[138]	Based on post-progression value published by van Agthoven et al 2004
Dead	0	0		

[a] Standard error, assumed to be 20% of the mean value.

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; LLoT, last line of treatment; PANO, panobinostat; SD, standard deviation.

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

Costs used within the model reflect the UK health service perspective and consisted of four components:

- Drug acquisition costs (including administration costs for bortezomib)
- Treatment monitoring cost
- Costs for management of adverse events
- Terminal care costs

No formal literature searches were performed to identify resource use or health care costs. Drug acquisition costs were taken from the British National Formulary (BNF) and administration costs for bortezomib were assumed to correspond to the costs of a nurse visit. (All other treatments require oral administration and therefore no administration costs were included). The tests performed and the frequency of monitoring during treatment were based on the assessments performed in the PANORAMA-1 study and were modified based on expert clinical opinion to reflect routine clinical practice in the UK. Costs of tests were taken from the National schedule of reference costs together with other publishes sources. Costs for management of adverse events were taken from those used in recent NICE submissions in oncology. Costs for terminal care were taken from the National Audit Office (2008)[143] and was applied for each deaths in the model along the treatment pathway.

5.5.2 Intervention and comparators' costs and resource use

Drug acquisition (and administration) costs

Drug acquisition costs were based on the most recent available list price and were extracted from the BNF (see Table 53) and the price for the panobinostat 20 mg tablet was set at £776 bortezomib is dosed per body surface area. The average body surface area was estimated to be 1.81 m^2, derived using a published formula[144] and utilizing the average weight (72 kg) and height (164 cm) of patients in the PANORAMA-1 trial. Table 53 summarises the unit cost and cost per administration for each drug.

Table 53 Unit cost and cost per administration for each drug

Drug	Unit	Unit cost	Dose	Cost/ dose	Source
Panobinostat	20 mg	£776	20 mg	£776	Assumption
Bortezomib	3.5 mg	£762.38	1.3 mg/m^2	£512.54	BNF
Dexamethasone	2 mg	£0.78	20/40 mg	£7.8 / £15.60	BNF
Lenalidomide	25 mg	£208.00	25 mg	£208.00	BNF
Pomalidomide	4 mg	£423.00	4 mg	£423.00	BNF

BNF, British National Formulary; for bortezomib vial sharing was assumed in line with UK clinical practice and also to account for the dose intensity as seen in the PANORAMA-1 trial.

Average drug costs per cycle were calculated for each regimen. As the PANO/BTZ/DEX and BTZ/DEX regimens are given as 3-weekly cycles, cost for other regimens were transformed to costs per 3-week cycle.

Treatment interruptions and subsequent dose reductions were allowed in the PANORAMA 1 trial. The average cost per cycle for PANO/BTZ/DEX and BTZ/DEX was calculated based on the mean dose intensity for each drug in PANORAMA-1 (see Table 54). The average cycle cost was £5,375 and £1,847 in the first treatment phase and £4,566 and £923.32 in the second treatment phase for PANO/BTZ/DEX and BTZ/DEX, respectively. In addition, the costs of drug administration were included for bortezomib. It was assumed that bortezomib is administered intravenously in all patients as in the PANORAMA-1 clinical trial. The cost associated with intravenous administration (£156) of bortezomib was assumed to be equal to the adult follow-up outpatient mandatory tariff price for speciality 303 Haematology [clinical] taken from the UK National Tariff 2013–2014. All other drugs are administered orally and were assumed to incur no administration costs.

Table 54 Mean dose intensity in the PANORAMA-1 trial

	Panobinostat	Bortezomib	Dexamethasone
PANO/BTZ/DEX	80.7%	75.8%	87.5%
BTZ/DEX	NA	86.7%	95.1%

BTZ, bortezomib; DEX, dexamethasone; NA, not applicable; PANO, panobinostat;

The cost of lenalidomide applied in the model was calculated as a weighted average of daily doses across all patient days in the MM-010 study. The cost of concomitant use of granulocyte colony-stimulating factor (G-CSF) was also included[14] in the cost of lenalidomide by assuming all patients received G-CSF after their first dose interruption. The resulting weighted average 28 days cycle cost for lenalidomide was £3,773 as published in the Single Technology Appraisal (STA) of lenalidomide for the treatment of MM in people who have received at least one prior therapy with bortezomib

[14] Concomitant use of granulocyte colony-stimulating factor (G-CSF) was applied by assuming all patients received lenalidomide,25 mg, with G-CSF after their first dose interruption (26.8% of the patients, £473.62 per patient 4-weekly cycle cost, ie £95 per 3-weekly cycle).

(TA171).[87] This average cycle cost was transformed into a 3-weekly cycle cost of £2,830. Because the manufacturer of lenalidomide has agreed a PAS with the Department of Health, in which the cost of lenalidomide for people who remain on treatment for more than 26 cycles (each of 28 days) is met by the manufacturer, in the model lenalidomide costs were only applied for 35 (ie ≈26*28/21) 3-weekly cycles. The cost for dexamethasone was £2.59 per 28-day cycle (ie £1.94 per 3-weekly cycle).

As with lenalidomide, the cost of pomalidomide applied in the model took into account dose interruptions. Depending on the treatment cycle, the estimated 28-day cycle cost varied between £7,375.09 and £8,884.00, as published in the STA of pomalidomide for rr MM.[131] For the economic model, the average of these costs was taken (ie £8,130) and was transformed into an average 3-weekly cycle cost (ie £6,097). The cost of dexamethasone was £2.17 per cycle (ie £1.63 per 3-weekly cycle). The cost of concomitant medications was included and estimated to be £22.63 per week (ie £67.89 per 3-weekly cycle).

Treatment costs for LLoT − beyond the costs associated to POM/DEX − were obtained from the study of Gooding et al[145] which was assumed to represent the typical treatment costs after third-line treatment in the UK. This study reported treatments given and further supportive care, ie medical-resource utilisation (MRU) costs for a cohort of double-refractory/intolerant patients with MM in the UK. Data on anti-myeloma therapies prescribed and MRU were obtained from a single centre in Oxford for 36 patients who had received four lines of treatment between 2011 and 2013. Median age at diagnosis for the cohort was 65.3 years (48 to 83 years). MRU (clinic attendance, inpatient admissions, supportive therapies, transfusions and blood tests) from start of fourth-line therapy until death or to the last follow-up were retrieved from health care records. When offered a choice of therapy, 77% of patients preferred an active treatment to care with palliative intent. Therapies were typically bendamustine-based regimens (53%), retreatment with bortezomib (10%) or lenalidomide-based regimens (27%). Patients received treatment for a mean of 15.3 weeks. The mean drug cost for fourth-line anti-MM therapy – excluding POM/DEX, which was not yet available at the time of the study – was £5,101 per patient (ie £1,001 per 3-weekly cycle), and the mean MRU cost during fourth-line therapy was £11,160 (ie £2,188 per 3-weekly cycle). For the purpose of the model, the average 3-weekly cost for supportive care was assumed to correspond to the average 3-weekly MRU cost.

The proportion of patients receiving any type of active treatment is assumed to be 77% in line with Gooding et al, of which 31.5 receive POM/DEX and 45.5% receive other active treatment as described by Gooding et al. The average 3 weekly cycle cost is derived from these treatments and equals with £4,586.

Table 55 Costs per 3-week cycle for regimens included in the model

Regimen	Cost per 3-week cycle	Comments
PANO/BTZ/DEX[15]	£5,375 (first treatment phase, cycles 1 to 8) £4,566 (second treatment phase, cycles 9 to 16)	IV administration cost of £156 per treatment to be added for BTZ
BTZ/DEX	£1,847 (first treatment phase, cycles 1 to 8) £923 (second treatment phase, cycles 9 to 16)	IV administration cost of £156 per treatment to be added for BTZ
LEN	£2,830	Applied for 35 3-weekly cycles Cost of DEX, £1.94 per cycle and G-CSF, £95 per 3-week cycle to be added
POM	£6,097	Cost of DEX, £1.63 per cycle and concomitant medications, £67.89 per cycle, to be added
Fourth-line therapy (other active treatments)	£1,001	Gooding et al.[145]
MRU	£2,188	Gooding et al.[145]

BTZ, bortezomib; DEX, dexamethasone; G-CSF, granulocyte colony-stimulating factor; IV, intravenous; LEN, lenalidomide; MRU, medical-resource utilisation; PANO, panobinostat; POM, pomalidomide.

Treatment monitoring costs

Monitoring costs were applied in the model for patients being in the pre-progression health states (ie pre-progression, Tx1 and pre-progression, no Tx1) but not for post-progression treatment (ie. third- and fourth-line) as a simplifying assumption. The treatment monitoring scheme used was adapted from the visit schedule and assessments scheme used by participating physicians in the PANORAMA-1 trial (see Table 56). The adapted scheme was validated by a clinical expert. This monitoring scheme was used to calculate average monitoring costs per 3-week cycle based on the unit costs summarised in Table 57. Monitoring costs were assumed to be the same for both PANO/BTZ/DEX and BTZ/DEX and estimated to be £171. Based on expert opinion, it was assumed that pre-progression patients who were not on treatment would receive regular monitoring on a 6-weekly basis, hence the average monitoring cost calculated per cycle was half of that applied while on treatment.

[15] Based on the base case panobinostat price assumption of £776 for the 20mg capsule

Table 56 Monitoring scheme for pre-progression therapy (PANO/BTZ/DEX or BTZ/DEX)

Activity	Frequency per cycle
Serum protein assessment	1.00
Skeletal survey (bone X-ray)	0.23
Lab results – haematology	1.00
Lab results – thyroid function test	1.00
Lab results – blood chemistry	1.00
Specialist visit	0.06

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

Table 57 Unit costs per monitoring activity

Activity	Unit cost	Source
Serum protein assessment	£15	NICE TA338, Pomalidomide
Skeletal survey (bone X-ray)	£75.00	2014, http://www.nice.org.uk/guidance/cg176/resources/cg176-head-injury-costing-template2
Lab results - Haematology	£3.00	2014, Directly Accessed Pathology Services, Haematology, National schedule of reference costs (2013–2014)
Lab results - Thyroid function test	£18.00	2014, http://www.nice.org.uk/guidance/ta312/resources/ta312-multiple-sclerosis-relapsingremitting-alemtuzumab-costing-template2
Lab results - Blood chemistry	£3.00	2014, Directly Accessed Pathology Services, Haematology, National schedule of reference costs (2013–2014)
Specialist visit	£156.00	2014, Outpatients - Consultant Led, Clinical haematology, National schedule of reference costs (2013–2014)

NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

5.5.3 Health-state unit costs and resource use

Table 58 List of health states and associated costs in the economic model

Health states	Items	Value	Reference in submission
A: Pre-progression, PANO/BTZ/DEX	PANO/BTZ/DEX[16]	£5,366 (first treatment phase, cycles 1 to 8) £4,562 (second treatment phase, cycles 9 to 16)	Section 5.5.2
	BTZ/DEX	£1,837 (first treatment phase, cycles 1 to 8) £918 (second treatment phase, cycles 9 to 16)	Section 5.5.2
	IV administration	£156	Section 5.5.2
	Monitoring and tests	£185.56	Section 5.5.2
	Adverse events	PANO/BTZ/DEX: £117.04	Section 5.5.4
	Total (PANO/BTZ/DEX)	£6,293 (cycle 1 to 8) £5,176 (cycle 9 to 16)	
	Total (BTZ/DEX)	£2763 (cycle 1 to 8) £1,533 (cycle 9 to 16)	
B: Pre-progression, No treatment	Monitoring costs	£185.56 / 2 = £92.78	Section 5.5.2
C and D: Post-progression, LEN/DEX, POM/DEX or BSC	LEN/DEX Concomitant med. POM/DEX Concomitant med. Other active treatments BSC	£2,831.69 £95.20 £6,098.63 £67.89 £1,001 £2,188	Section 5.5.2
E: Death	Terminal care	£1,235 lump sum applied on death	Section 5.5.5

BSC, best supportive care; BTZ, bortezomib; DEX, dexamethasone; IV, intravenous; LEN, lenalidomide; PANO, panobinostat; POM, pomalidomide.

5.5.4 Adverse reaction unit costs and resource use

Costs for management of adverse events were applied in the model to patients receiving pre-progression treatment (ie PANO/BTZ/DEX or BTZ/DEX) but not for post-progression treatment (ie

[16] Based on the base case panobinostat price assumption of £776 for the 20mg capsule

third- and fourth-line). Estimated 3-weekly costs were determined from adverse event occurrence probabilities and management costs for the ten most frequently occurring grade 3/4 adverse events reported in PANORAMA-1.

Adverse event costs

Daily adverse event occurrence rates in patients receiving PANO/BTZ/DEX or BTZ/DEX were estimated as the number of patients for whom grade 3/4 adverse events were documented divided by the total treatment exposure time expressed in patient-days (see Table 59). The daily adverse event rates were then transformed into 3-weekly occurrence rates by multiplying daily rates by 21, and subsequently into 3-weekly probabilities by transforming rates into probabilities (probability = 1 – exp(-rate).

Table 59 Adverse events as observed in the full PANORAMA-1 trial population (safety set)

	PANO/BTZ/DEX (n = 381)		**BTZ/DEX (n = 377)**	
Mean study treatment exposure, days	183.5		195.0	
Total exposure time to treatment, patient-days	69,913.5		73,515	
Grade 3/4 AEs	**N**	**3-weekly occurrence probability**	**N**	**3-weekly occurrence probability**
Anaemia	63	0.0063	60	0.0057
Asthenia	36	0.0036	14	0.0013
Diarrhoea	97	0.0097	30	0.0029
Fatigue	65	0.0065	33	0.0031
Hypokalaemia	73	0.0073	24	0.0023
Hyponatraemia	37	0.0037	13	0.0012
Lymphopenia	35	0.0035	12	0.0011
Neutropenia	92	0.0092	30	0.0029
Pneumonia	48	0.0048	39	0.0037
Thrombocytopenia	217	0.0217	94	0.0089

AEs, adverse events; BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; N, number of patients with AE.

Management costs of the ten most frequently reported grade 3/4 adverse events were obtained from various sources including the latest NICE reference cost document, previous NICE submission dossiers, or published literature. These are presented in Table 60. Only direct costs were taken into account and no differentiation was made between inpatient and outpatient management costs.

Table 60 Costs per adverse event

Grade 3 and 4 adverse events	Unit cost	Source
Anaemia	£1,155	2014, Non-Elective Inpatients – Long Stay, Iron Deficiency Anaemia (SA04L), National schedule of reference costs (2013-2014)
Asthenia	£12	2013, TA316
Diarrhoea	£623	2013, TA316
Fatigue	£12	2013, TA316
Hypokalaemia	£355	2014, High Cost Drugs, Intravenous Nutrition, Band 1 (XD26Z), National schedule of reference costs (2013–2014)
Hyponatraemia	£355	Assumed to be the same as Hypokalaemia
Lymphopenia	£167	Assumed to be the same as Neutropenia
Neutropenia	£167	2014, High Cost Drugs,Neutropenia Drugs, Band 1 (XD25Z), National schedule of reference costs (2013–2014)
Pneumonia	£1,433	2014, Non-Elective Inpatients – Long Stay, Atypical or Viral Pneumonia (DZ11J), National schedule of reference costs (2013–2014)
Thrombocytopenia	£604	2013, Non-Elective Inpatients – Short Stay, Thrombocytopenia (SA12K), National schedule of reference costs (2013–2014)

To estimate the 3-weekly adverse event costs for PANO/BTZ/DEX and BTZ/DEX, the cost for each adverse event was multiplied by the corresponding 3-weekly adverse event occurrence probability and the total was derived by summing the 3-weekly costs for each of the ten adverse events. The resulting overall costs (PANO/BTZ/DEX, £117.04; BTZ/DEX, £63.48) were applied in every 3-week cycle of the treatment for patients in Health state A (pre-progression on treatment).

5.5.5 Miscellaneous unit costs and resource use

Terminal care costs

A one-off terminal cost of £1,235 is applied in the model when a patient dies, adopting the calculations published in the STA of lenalidomide for rrMM.[87] Costs of terminal care in the UK have been estimated to be £6,177. For the purpose of the model, it was assumed that 20% of the patients that die actually receive terminal care (ie it is assumed that 20% of patients use hospital services.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of base-case de novo analysis inputs

Table 61 summarises the variables used in the analysis.

Table 61 Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
PANO/BTZ/DEX			
Risk of progression or death, *constant*	–3.837 (Figure 38)	–4.266 to –3.408, MVN	Section 5.3.2
Risk of progression or death, *log(p)*	0.201 (Figure 38)	0.093 to 0.309, MVN	Section 5.3.2
Risk of progression (and risk of death), *constant*	1.075 (Figure 39)	0.015 to 2.134, MVN	Section 5.3.2
Risk of progression (and risk of death), *log-cycle*	–1.658 (Figure 39)	–2.254 to -1.061, MVN	Section 5.3.2
Risk of treatment discontinuation, *constant*	2.031 (Figure 40)	1.893 to 2.168, MVN	Section 5.3.2
Risk of treatment discontinuation, *ln(gamma)*	–0.249 (Figure 40)	–0.148 to -0.181, MVN	Section 5.3.2
BTZ/DEX (applied for cycle 1 to 4)			
Risk of progression or death, *constant*	–3.545 (Figure 38)	–3.917 to -3.173, MVN	Section 5.3.2
Risk of progression or death, *log(p)*	0.241 (Figure 38)	0.146 to 0.336, MVN	Section 5.3.2
Risk of progression (and risk of death), *constant*	–0.727 (Figure 39)	–1.724 to 0.270, MVN	Section 5.3.2
Risk of progression (and risk of death), *cycle*	–0.301 (Figure 39)	–0.482 to -0.120, MVN	Section 5.3.2
Risk of treatment discontinuation, *constant*	2.164 (Figure 40)	2.042 to 2.287, MVN	Section 5.3.2
Risk of treatment discontinuation, *ln(gamma)*	–0.369 (Figure 40)	–0.472 to -0.267, MVN	Section 5.3.2
BTZ/DEX (responders)			
Risk of progression or death, *constant*	–-4.185 (Figure 38)	–4.800 to -3.569, MVN	Section 5.3.2
Risk of progression or death, *log(p)*	0.373 (Figure 38)	0.237 to 0.509, MVN	Section 5.3.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Risk of progression (and risk of death), *constant*	–0.093 (Figure 39)	–2.248 to 2.063, MVN	Section 5.3.2
Risk of progression (and risk of death), *log-cycle*	–2.131 (Figure 39)	–3.707 to –0.555, MVN	Section 5.3.2
Risk of treatment discontinuation, *constant*	–2.830 (Figure 40)	–3.044 to –2.616, normal	Section 5.3.2
BTZ/DEX discontinuing treatment during cycles 1 to 4 without disease progression			
Risk of progression, *constant*	–2.019 (Figure 41)	–2.639 to –1.400, normal	Section 5.3.2
Risk of death, *constant*	–4.412 (Figure 41)	–5.289 to –3.536, normal	Section 5.3.2
BTZ/DEX discontinuing treatment during cycles 5 to 8 without disease progression			
Risk of progression, *constant*	–2.809 (Figure 42)	–3.462 to –2.156, normal	Section 5.3.2
Risk of death, *constant*	–3.959 (Figure 42)	–4.700 to –3.218, normal	Section 5.3.2
Post-progression phase			
Risk of progression on LEN/DEX, *median PFS*	11.1 months (Figure 45)	9.63 to 12.57, normal	Section 5.3.3
Risk of post-progression death (progression during cycles 1 to 4), constant	–3.122 (Figure 47)	–3.688 to –2.556, normal	Section 5.3.3
Risk of post-progression death (progression during cycles 5+), constant	–3.972 (Figure 47)	–4.336 to 3.608, normal	Section 5.3.3
Response to treatment at cycle 4 (BTZ/DEX)			
Response, %	0.551 (Figure 43)	0.499 to 0.606, beta	Section 5.3.2
Adverse events (PANO/BTZ/DEX)			
Anaemia, %	0.019 (Table 59)	0.012 to 0.027, beta	Section 5.5.4
Asthenia, %	0.011 (Table 59)	0.007 to 0.015, beta	Section 5.5.4
Diarrhoea, %	0.029 (Table 59)	0.018 to 0.041, beta	Section 5.5.4
Fatigue, %	0.019 (Table 59)	0.012 to 0.028, beta	Section 5.5.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Hypokalaemia, %	0.022 (Table 59)	0.014 to 0.031, beta	Section 5.5.4
Hyponatraemia, %	0.011 (Table 59)	0.007 to 0.016, beta	Section 5.5.4
Lymphopenia, %	0.014 (Table 59)	0.009 to 0.020 beta	Section 5.5.4
Neutropenia, %	0.027 (Table 59)	0.017 to 0.039, beta	Section 5.5.4
Pneumonia, %	0.014 (Table 59)	0.009 to 0.021, beta	Section 5.5.4
Thrombocytopenia, %	0.065 (Table 59)	0.040 to 0.091, beta	Section 5.5.4
Adverse events (BTZ/DEX)			
Anaemia, %	0.017 (Table 59)	0.011 to 0.024, beta	Section 5.5.4
Asthenia, %	0.004 (Table 59)	0.003 to 0.006, beta	Section 5.5.4
Diarrhoea, %	0.009 (Table 59)	0.005 to 0.012, beta	Section 5.5.4
Fatigue, %	0.009 (Table 59)	0.006 to 0.013, beta	Section 5.5.4
Hypokalaemia, %	0.007 (Table 59)	0.004 to 0.010, beta	Section 5.5.4
Hyponatraemia, %	0.004 (Table 59)	0.002 to 0.005, beta	Section 5.5.4
Lymphopenia, %	0.008 (Table 59)	0.005 to 0.011, beta	Section 5.5.4
Neutropenia, %	0.009 (Table 59)	0.005 to 0.012, beta	Section 5.5.4
Pneumonia, %	0.011 (Table 59)	0.007 to 0.016, beta	Section 5.5.4
Thrombocytopenia, %	0.027 (Table 59)	0.017 to 0.038, beta	Section 5.5.4
Utilities (3-weekly)			
Pre-progression, PANO/BTZ/DEX	0.041 (Table 49)	0.040 to 0.041, beta	Section 5.4.5
Pre-progression, BTZ/DEX	0.042 (Table 49)	0.041 to 0.042, beta	Section 5.4.5
Post-progression, Further treatments	0.038 (Table 49)	0.037 to 0.038, beta	Section 5.4.5
Pre-progression, no treatment	0.044 (Table 49)	0.043 to 0.045, beta	Section 5.4.5
Costs			
IV administration of BTZ	£156	£101 to £223, gamma	Section 5.5.2
Serum protein assessment	£15 (Table 57)	£10 to £22, gamma	Section 5.5.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Skeletal survey (bone X-ray)	£75 (Table 57)	£49 to £107, gamma	Section 5.5.2
Lab results – haematology	£3 (Table 57)	£2 to £4, gamma	Section 5.5.2
Lab results – thyroid function test	£18 (Table 57)	£12 to £26, gamma	Section 5.5.2
Lab results – blood chemistry	£3 (Table 57)	£2 to £4, gamma	Section 5.5.2
Visit	£156 (Table 57)	£101 to £223, gamma	Section 5.5.2
Anaemia	£1,155 (Table 60)	£748 to £1,650, gamma	Section 5.5.4
Asthenia	£12 (Table 60)	£8 to £81, gamma	Section 5.5.4
Diarrhoea	£623 (Table 60)	£403 to £890, gamma	Section 5.5.4
Fatigue	£12 (Table 60)	£8 to £18, gamma	Section 5.5.4
Hypokalaemia	£355 (Table 60)	£230 to £507, gamma	Section 5.5.4
Hyponatraemia	£355 (Table 60)	£230 to £507, gamma	Section 5.5.4
Lymphopenia	£167 (Table 60)	£108 to £239, gamma	Section 5.5.4
Neutropenia	£167 (Table 60)	£108 to £239, gamma	Section 5.5.4
Pneumonia	£1,433 (Table 60)	£927 to £2,046, gamma	Section 5.5.4
Thrombocytopenia	£604 (Table 60)	£391 to £862, gamma	Section 5.5.4
BSC	£2,188 (Table 60)	£1,416 to £3,126, gamma	Section 5.5.4
Other active treatments	£1,001 (Table 60)	£648 to £1,430, gamma	Section 5.5.4
Terminal care	£1,235 (section 5.5.5)	£799 to £1,765, gamma	Section 5.5.5

BTZ, bortezomib; DEX, dexamethasone; CI, confidence interval, IV, intravenous; LEN, lenalidomide; MVN, multivariate normal; PANO, panobinostat; TTP, time to progression

5.6.2 Assumptions

The key assumptions of used in the model and their justifications are summarised in Table 62.

Table 62 key assumptions of used in the model and their justification

Assumption	Justification
1) Patients experiencing progression on PANO/BTZ/DEX or BTZ/DEX proceed to receive LEN/DEX	Current UK treatment guidelines recommend that patients at second or subsequent relapse should be considered for LEN[51] Analysis of current treatment patterns in the UK indicates that most patients who relapse following the second-line BTZ-based therapy receive LEN/DEX[17] NICE guidance (TA171) recommends LEN/DEX as an option for patients who have received at least two prior therapies.[87]
2) Patients experiencing progression on LEN/DEX receive POM/DEX or other active treatments together with supportive care until they die	POM/DEX is approved for treatment of patients who have received at least two prior treatment regimens, including both LEN and BTZ, and have demonstrated disease progression on the last therapy.[146] POM/DEX is recommended in the BCSH guidelines and the National Chemotherapy Algorithm for Multiple Myeloma (v.0.7) as an option for patients following LEN/DEX and is reimbursed in this setting by the NCDF.[51,79,89]
3) Costs associated with fourth-line treatment other than POM/DEX were assumed to correspond to those reported by Gooding et al, a study of fourth-line therapy in a single UK centre[145]	Gooding et al presents costs for fourth-line therapy in a single UK centre between 2011 and 2013 and is believed to be representative of current fourth-line therapy in England and Wales, other than the use of POM/DEX which was not available at the time of the study
4) Mortality risk is applied exclusively from the trial. No distinction is made between mortality related to MM or unrelated to MM.	Given the short life expectancy of patients with rrMM, only trial data were used to model the OS of patients, i.e. no general population mortality was considered additionally.
5) BTZ as part of PANO/BTZ/DEX and BTZ/DEX is assumed to be administered intravenously.	Reflecting use in PANORAMA-1 clinical trial and current clinical practice.
6) More frequent monitoring activity is required while on treatment than during the treatment free interval.	Clinical expert opinion advised that less frequent monitoring is used when off treatment
7) HRQL for patients in the pre-progression, no treatment health state is assumed to be equal to that of patients during the last cycle of pre-progression treatment (ie cycle 16 for PANO/BTZ/DEX or BTZ/DEX).	The value used is higher than the mean for the overall treatment phase as expected given that HRQL has been shown to be better when off treatment[23]
8) When second-line BTZ +/- DEX is discontinued due to reasons other than	Reflects current clinical practice in the UK

[17] In the UK, based on a retrospective audit of 1645 patients performed by the HMRN, 65% of the patients received a lenalidomide based regimen as a third-line option after receiving a bortezomib based regimen as a prior treatment, ie as second-line therapy.

progression or death, a treatment free interval is considered only in case of patients achieving at least a PR	

BCSH, British Committee for Standards in Haematology; BTZ, bortezomib; DEX, dexamethasone; HRQL, health-related quality of life; LEN, lenalidomide; MM, multiple myeloma; NCDF, National Cancer Drugs Fund; NICE, National Institute for Health and Care Excellence; OS, overall survival; PANO, panobinostat; POM, pomalidomide; rrMM, relapsed/refractory multiple myeloma..

5.7 Base-case results

5.7.1 Base-case incremental cost effectiveness analysis results

Table 63 Base-case results with multiple price scenarios[18]

Base case: assuming £776 per 20 mg capsule

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
PANO/BTZ/DEX	£197,922	3.570	2.404	£44,487	0.773	0.563	£79,025	£79,025
BTZ/DEX	£153,434	2.797	1.841					

BTZ, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PANO, panobinostat; QALYs, quality-adjusted life years

[18] Currently there is no approved price for panobinostat. Final price to be expected upon granting of EMA marketing authorisation.

5.7.2 Clinical outcomes from the model

Table 64 presents the median PFS and median OS estimates of the cost-effectiveness model for PANO/BTZ/DEX. While the median PFS is replicated virtually perfectly, the predicted median OS is longer than in the trial. It is so because the post-progression OS is based on data from patients that received LEN/DEX as post-progression treatment and not based on data from the full population. Bortezomib clinical trial efficacy results were not tested against the modelled outcomes as the model includes assumptions on the treatment pathway taken from UK clinical practice and bortezomib label (ie stopping rules).

Table 64 Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
Median PFS (PANO/BTZ/DEX)	12.0 months	12.0 months
Median OS (PANO/BTZ/DEX)	33.6 months	38.3 months
Proportion of patients experiencing adverse events (PANO/BTZ/DEX)	Rates obtained from trial	Rates obtained from trial

BTZ, bortezomib; DEX, dexamethasone;OS, overall survival; PANO, panobinostat; PFS, progression-free survival.

5.7.3 Disaggregated results of the base case incremental cost effectiveness analysis

Table 65 below provide an overview of the discounted QALYs, respectively, patients can expect to spend in the different health states of the model. Patients receiving PANO/BTZ/DEX can expect to have more QALYs than patients receiving BTZ/DEX, which is mainly due to the longer PFS for PANO/BTZ/DEX and the due to the PAS for BTZ/DEX, resulting in longer treatment-free period for patients receiving PANO/BTZ/DEX (incremental QALY for the no treatment health state is 0.38). During the post-progression phase the total QALY gain slightly further increases (incremental QALYs 0.05). Overall, patients receiving PANO/BTZ/DEX expect to live 2.40 discounted QALYs whereas patients receiving BTZ/DEX expect to live 1.84 discounted QALYs, resulting in an estimated incremental QALYs of 0.56.

Table 65 Summary of QALY gain by health state

Health state	QALY intervention (PAN/BTZ/DEX)	QALY comparator (BTZ/DEX)	Increment	Absolute increment	% absolute increment
Pre-progression, treatment	0.353	0.218	0.135	0.135	24%
Pre-progression, No treatment	0.536	0.155	0.381	0.381	68%
Post-progression, LEN/DEX	0.734	0.734	0.000	0.000	0%
Post-progression, LLoT	0.780	0.732	0.048	0.048	8%
Total	**2.404**	**1.841**	**0.563**	**0.564**	**100%**

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

BTZ, bortezomib; DEX, dexamethasone, LEN, lenalidomide, LLoT, last line of treatment; PANO, panobinostat; QALY, quality-adjusted life year.

The total cost is higher for the PANO/BTZ/DEX treatment arm (£204,386 discounted) than for the BTZ/DEX treatment arm (£166,508 discounted) yielding an incremental cost of £37,878. Higher PANO/BTZ/DEX drug costs (£34,952) contribute to most of the incremental costs. Most costs are generated during the last treatment; this is the health state in that patients spend the most time.

Table 66 Summary of costs by health state

Base case: assuming £776 per 20 mg capsule

Health state	Cost intervention (PAN/BTZ/DEX)	Cost comparator (BTZ/DEX)	Increment	Absolute increment	% absolute increment
Pre-progression, treatment	£52,552	£14,708	£37,843	£37,843	85%
Pre-progression, No treatment	£1,132	£328	£804	£804	2%
Post-progression, LEN/DEX	£46,256	£46,303	-£47	£47	0%
Post-progression, LLoT	£96,898	£90,978	£5,920	£5,920	13%
Death	£1,084	£1,117	-£33	£33	0%
Total	**£197,922**	**£153,434**	**£44,487**	**£44,648**	**100%**

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

BTZ, bortezomib; DEX, dexamethasone, LEN, lenalidomide,LLoT, last line of treatment; PANO, panobinostat; QALY, quality-adjusted life year

Table 67 Summary of predicted resource use by category of cost

Base case: assuming £776 per 20 mg capsule

Item	Cost intervention (PAN/BTZ/DEX	Cost comparator (BTZ/DEX)	Increment	Absolute increment	% absolute increment
Drug costs	£48,577	£12,593	£35,984	£35,984	81%
Tests and monitoring (on treatment)	£2,960	£1,783	£1,177	£1,177	3%
Tests and monitoring (off treatment)	£1,132	£328	£804	£804	2%
LEN/DEX	£46,256	£46,303	-£47	£47	0%
LLoT	£96,898	£90,978	£5,920	£5,920	13%
Adverse events	£1,014	£333	£681	£681	2%
Terminal care	£1,084	£1,117	-£33	£33	0%
Total	**£197,922**	**£153,434**	**£44,487**	**£44,648**	**100%**

DEX, dexamethasone, LEN, lenalidomide; LLoT, last line of treatment

5.8 Sensitivity analyses

The economic model has numerous parameters which are integral to provide the model outcomes. To determine which parameters have the greatest impact on the model outcomes, further analyses are required. Hence, sensitivity analyses were used to investigate how sensitive a model is to changes from the deterministic input parameter values. Uncertainty margins were applied to each input parameter of interest based on corresponding margins provided in literature or based on assumptions if information was unavailable.

In particular, the cost-effectiveness model accommodated three different ways of assessing the impact of input parameter uncertainty on the model outcomes. These included deterministic (or univariate) sensitivity analyses, probabilistic sensitivity analyses, and scenario analyses:

- Deterministic sensitivity analyses were used to determine the drivers of the model outcomes;
- Probabilistic sensitivity analysis were used to display how the combined uncertainty of all input parameters translates into the overall uncertainty of the model outcomes;

- Scenario analyses were used to assess the impact of certain model settings on the results that were not subject to the deterministic sensitivity analyses (eg time horizon of the model, alternative input parameter choices).

The deterministic (or univariate) sensitivity analyses and probabilistic sensitivity analyses were pre-programmed using Microsoft® Visual Basic for Applications (VBA) with their inputs defined in the input parameters worksheets. The scenario analyses were performed manually.

5.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses were implemented to determine the extent of uncertainty around the ICER estimates. Random values were generated for specific parameter within a specified uncertainty distribution. This was performed for each parameter simultaneously and the resulting ICER was recorded, constituting one 'simulation'. One thousand simulations were performed, providing a distribution (and uncertainty estimates) of ICERs. Correlation between parameters were taken into account if parameters were simulated from a multivariate normal distribution.

For the probability of events occurring (such as the probability of adverse events), a beta distribution was applied to restrict values to between 0 and 1, in the same way that probabilities operate. For OS, PFS, progression to third-line therapy, and time to discontinuation Cholesky decomposition was used to account for the correlation between the regression parameters. A gamma distribution was fitted to costs only, as opposed to both resource use and costs - gamma distribution cannot fall below zero (but is otherwise unrestricted). The standard error of each parameter was the same as presented for the univariate sensitivity analyses. The distributions around specific parameters together with the deterministic estimates are presented in Table 61

Although the probabilistic sensitivity analyses is conducted in a Bayesian framework, there are three principles as well as explicit judgements that are taken into account when a distribution is selected:

- The nature of the parameter itself
- The way the parameter was estimated
- Decision context.

Application of these general principles means that there will be only a very limited choice of appropriate distributional forms for the input parameters. Where a probability is estimated from a proportion, the beta distribution is the natural choice. If the probability parameter is estimated from a logistic regression / Cox regression, then the parameters of interest are the coefficients on the log-odds / log-hazard scale.[147] For cost input data, gamma or lognormal distributions are typically chosen because these functions usually well describe the distribution of costs in real life[148] and because these distributions do not allow negative costs.

Not all model parameters were subject to probabilistic sampling in the probabilistic sensitivity analyses. Variables that were derived from other parameters did not vary directly; their values varied because they were related to input parameters that were subject to probabilistic sampling. Structural model parameters (eg time horizon of the model) and the unit costs (including the cost of panobinostat) were not included in the probabilistic sensitivity analyses either. Finally, model settings that have been selected based on regulatory guidelines (eg dosing and discount rates) were held fixed as well.

As

Figure 49 shows, at a willingness-to-pay threshold of £78,000/QALY (using the base case price) and , the probability of PANO/BTZ/DEX being cost-effective is estimated to be 50%. At a willingness-to-pay threshold of £20,000/QALY, £30,000/QALY, £50,000/QALY, and £100,000/QALY, this probability is estimated to be 0%, 0%, 0%, 97%, respectively, using the base case price and 0%, 0%, 7%, 100%, respectively, using the lower price.

The probabilistic sensitivity analysis resulted in the following 95% CIs around key model outcomes that are presented in Table 68.

Table 68. Values and 95% confidence intervals around key model outcomes

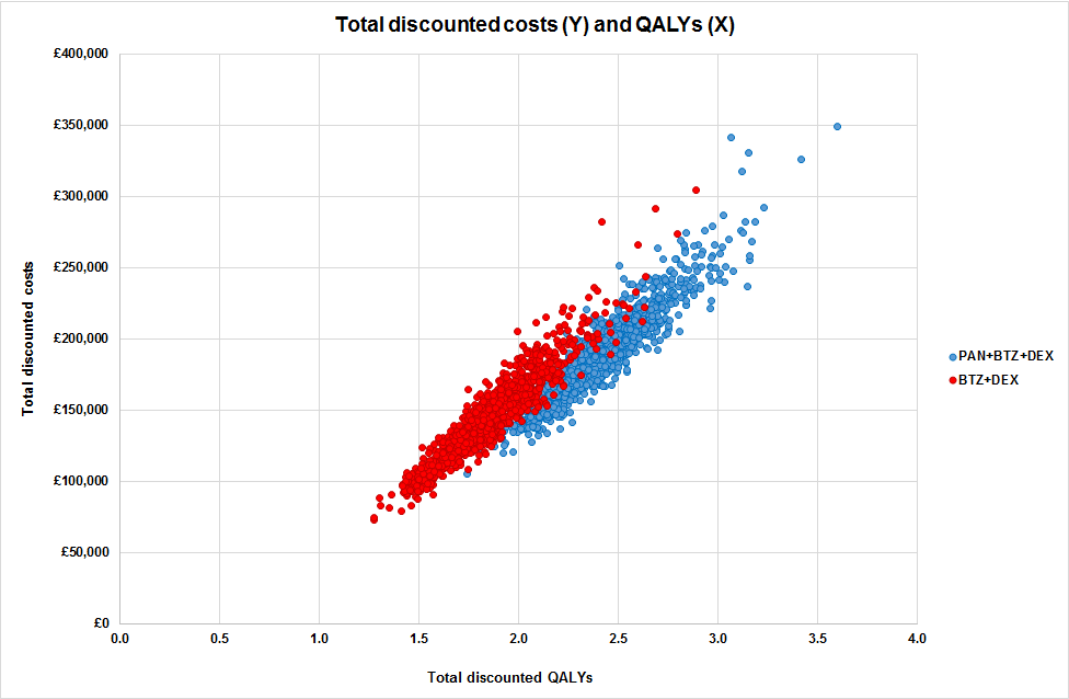
Base case: assuming £776 per 20 mg capsule

	Cost	Incremental cost	QALYs	Incremental QALY	ICER (QALY)
PANO/BTZ/DEX	£199,405 (£140,614 to £271,621)	£44,144 (£33,962 to £56,360)	2.40 (1.97 to 3.01)	0.56 (0.39 to 0.72)	£79,025
BTZ/DEX	£155,261 (£100,547 to £225,395)		1.86 (1.47 to 2.38)		

BTZ, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PANO, panobinostat; QALYs, quality-adjusted life years

Figure 47 Scatter plot of simulated total QALYs versus total costs for PANO/BTZ/DEX and BTZ/DEX (probabilistic sensitivity analysis), discounted analysis

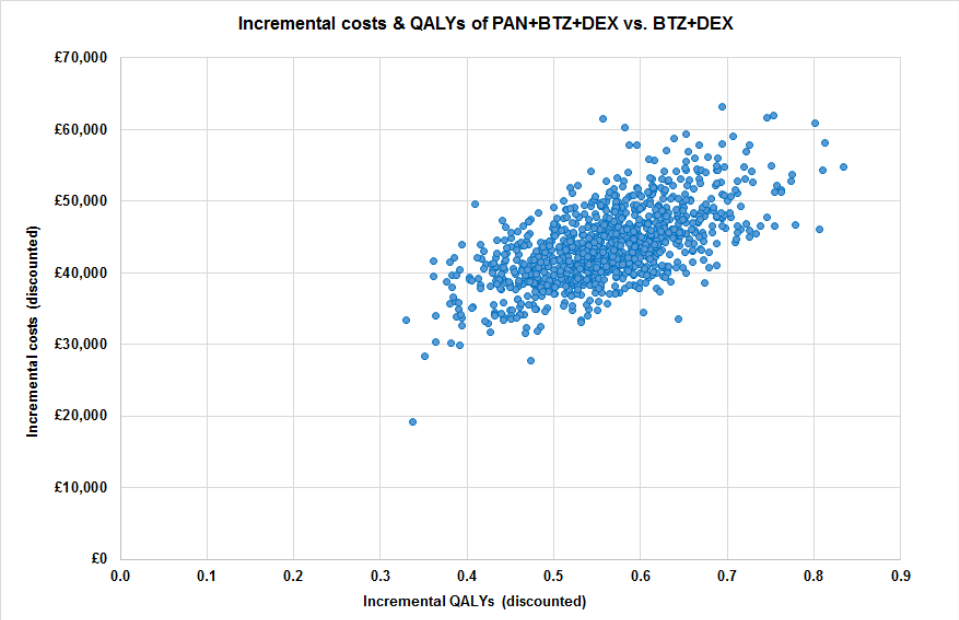
Base case: assuming £776 per 20 mg capsule



BTZ, bortezomib; DEX, dexamethasone; PAN(O), panobinostat; QALYs, quality-adjusted life years

Figure 48 Simulated total incremental QALYs versus incremental costs of PANO/BTZ/DEX and BTZ/DEX (probabilistic sensitivity analysis), discounted analysis

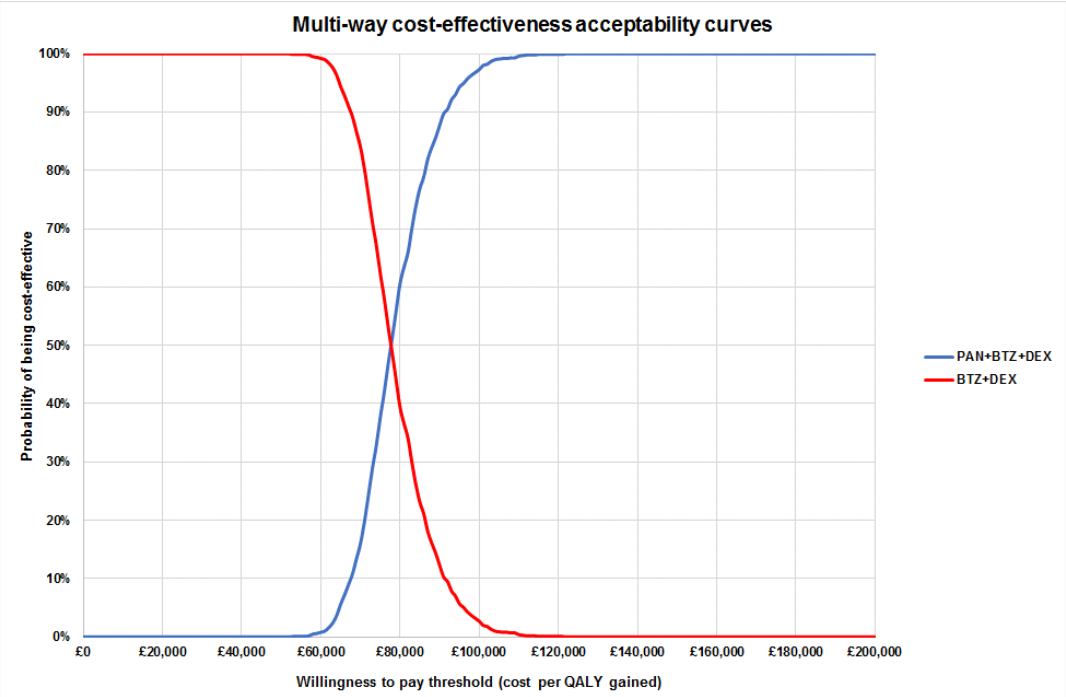
Base case: assuming £776 per 20 mg capsule



BTZ, bortezomib; DEX, dexamethasone; PAN(O), panobinostat; QALYs, quality-adjusted life years

Figure 49 Multi-way cost-effectiveness acceptability curves for PANO/BTZ/DEX and BTZ/DEX, discounted analysis

Base case: assuming £776 per 20 mg capsule



BTZ, bortezomib; DEX, dexamethasone; PAN(O), panobinostat; QALYs, quality-adjusted life years

Figure 50 Cost effectiveness acceptability frontier for PANO/BTZ/DEX and BTZ/DEX, discounted analysis

Base case: assuming £776 per 20 mg capsule

BTZ, bortezomib; DEX, dexamethasone; PAN(O), panobinostat; QALYs, quality-adjusted life years

5.8.2 Deterministic sensitivity analysis

In the current model structure, deterministic sensitivity analyses were generated using the upper and lower bounds of the 95% CI of each input parameter at a time. If the CI was not reported in the study from which a particular input parameter was derived, ± 2 times 20% of the mean (ie SD) value of the input parameter was assumed as the upper and lower limit of the CI. Such practice is well accepted if uncertainty margins around an input parameter are unavailable. The upper and lower limits for specific parameters included are presented in Table 61.

Table 69 presents the results of the deterministic sensitivity analyses for life years, QALY, and costs. In general, the model outcomes (ie QALYs, costs, and ICERs) are most sensitive to the regression parameters associated with progression (ie PFS, proportion of progressors). With respect to incremental QALYs, important driver was the utility values applied for the treatment free health state. With respect to incremental costs, progression-related parameters and treatment discontinuation rates appear to impact the results significantly whereas other input parameters did not show to be important determinants. In general, cost-related parameters did not influence the model results.

Table 69 Deterministic sensitivity analyses results

Base case: assuming £776 per 20 mg capsule

	PANO/BTZ/DEX			BTZ/DEX			Incremental			ICER		
	LYs	QALYs	Costs	LYs	QALYs	Costs	LYs	QALYs	Costs	LY	QALY	% (QALY)
Clinical parameters related[19]												
PFS, LCI	4.878	3.399	£201,277	2.965	1.959	£159,488	1.914	1.440	£41,789	£21,839	£29,015	-63%
PFS, UCI	2.839	1.866	£185,769	2.571	1.683	£143,926	0.267	0.183	£41,843	£156,648	£228,683	189%
Progression, LCI	3.684	2.477	£204,230	2.839	1.868	£155,499	0.845	0.609	£48,731	£57,676	£79,998	1%
Progression, UCI	2.917	1.986	£158,979	2.598	1.713	£142,493	0.319	0.273	£16,486	£51,663	£60,469	-23%
Discontinuation, LCI	3.570	2.406	£194,429	2.798	1.841	£153,729	0.771	0.565	£40,700	£52,762	£72,092	-9%
Discontinuation, UCI	3.570	2.402	£200,880	2.796	1.840	£153,000	0.774	0.562	£47,880	£61,847	£85,265	8%
Death risk,, off-Tx, c4, LCI	3.570	2.404	£197,922	2.811	1.850	£154,171	0.759	0.554	£43,750	£57,662	£79,007	0%
Death risk,, off-Tx, c4, UCI	3.570	2.404	£197,922	2.769	1.822	£151,952	0.801	0.581	£45,969	£57,401	£79,061	0%
Death risk,, off-Tx, c8, LCI	3.570	2.404	£197,922	2.876	1.894	£157,061	0.693	0.510	£40,861	£58,942	£80,190	1%
Death risk,, off-Tx, c8, UCI	3.570	2.404	£197,922	2.683	1.764	£148,211	0.887	0.640	£49,710	£56,031	£77,690	-2%
Death risk, LEN/DEX, c1-4, LCI	3.627	2.440	£202,349	2.908	1.912	£162,122	0.718	0.528	£40,227	£56,020	£76,190	-4%
Death risk, LEN/DEX, c1-4, UCI	3.536	2.382	£196,884	2.730	1.798	£151,399	0.805	0.584	£45,485	£56,478	£77,908	-1%
Death risk, LEN/DEX, c5+, LCI	3.698	2.486	£208,123	2.882	1.895	£160,167	0.816	0.591	£47,956	£58,742	£81,159	3%
Death risk, LEN/DEX, c5+, UCI	3.482	2.347	£190,938	2.739	1.803	£148,825	0.743	0.544	£42,113	£56,692	£77,439	-2%
Risk of prog, off Tx, c4, LCI	3.570	2.404	£197,922	2.805	1.849	£152,438	0.765	0.555	£45,484	£59,474	£81,979	4%
Risk of prog, off Tx, c4, UCI	3.570	2.404	£197,922	2.792	1.836	£154,039	0.778	0.568	£43,883	£56,437	£77,274	-2%
Risk of prog, off Tx, c8, LCI	3.570	2.404	£197,922	2.796	1.849	£148,722	0.774	0.554	£49,199	£63,595	£88,806	12%
Risk of prog, off Tx, c8, UCI	3.570	2.404	£197,922	2.798	1.834	£156,884	0.772	0.569	£41,037	£53,154	£72,059	-9%
Risk of prog, LEN/DEX, LCI	3.570	2.404	£204,761	2.797	1.841	£160,262	0.773	0.563	£44,500	£57,588	£79,047	0%
Risk of prog, LEN/DEX, UCI	3.570	2.404	£191,762	2.797	1.841	£147,674	0.773	0.563	£44,088	£57,055	£78,316	0%
Response at c4, LCI	3.570	2.404	£197,922	2.789	1.833	£153,981	0.781	0.571	£43,941	£56,268	£76,978	-3%
Response at c4, UCI	3.570	2.404	£197,922	2.806	1.849	£152,860	0.764	0.555	£45,061	£58,972	£81,238	3%
Utility-related												
PANO/BTZ/DEX, LCI	3.570	2.399	£197,922	2.797	1.841	£153,434	0.773	0.558	£44,487	£57,572	£79,676	1%
PANO/BTZ/DEX, UCI	3.570	2.408	£197,922	2.797	1.841	£153,434	0.773	0.567	£44,487	£57,572	£78,459	-1%
BTZ/DEX, LCI	3.570	2.404	£197,922	2.797	1.838	£153,434	0.773	0.566	£44,487	£57,572	£78,641	0%

[19] If not specified otherwise, test applied on all parametric models of the kind (e.g. PFS, LCI assessed the impact of setting all parameters of all three PFS

BTZ/DEX, UCI	3.570	2.404	£197,922	2.797	1.843	£153,434	0.773	0.560	£44,487	£57,572	£79,374	0%
Off-Tx, LCI	3.570	2.388	£197,922	2.797	1.836	£153,434	0.773	0.552	£44,487	£57,572	£80,591	2%
Off-Tx, UCI	3.570	2.419	£197,922	2.797	1.845	£153,434	0.773	0.574	£44,487	£57,572	£77,546	-2%
Later LOT, LCI	3.570	2.370	£197,922	2.797	1.808	£153,434	0.773	0.562	£44,487	£57,572	£79,174	0%
Later LOT, UCI	3.570	2.439	£197,922	2.797	1.875	£153,434	0.773	0.564	£44,487	£57,572	£78,868	0%
Costs-related												
BSC, LCI	3.570	2.404	£181,605	2.797	1.841	£138,115	0.773	0.563	£43,491	£56,282	£77,255	-2%
BSC, UCI	3.570	2.404	£217,735	2.797	1.841	£172,037	0.773	0.563	£45,698	£59,139	£81,176	3%
Other active Tx, LCI	3.570	2.404	£194,528	2.797	1.841	£150,248	0.773	0.563	£44,280	£57,304	£78,657	0%
Other active Tx, UCI	3.570	2.404	£202,046	2.797	1.841	£157,307	0.773	0.563	£44,739	£57,899	£79,473	1%
Terminal care, LCI	3.570	2.404	£197,539	2.797	1.841	£153,040	0.773	0.563	£44,499	£57,588	£79,046	0%
Terminal care, UCI	3.570	2.404	£198,386	2.797	1.841	£153,913	0.773	0.563	£44,473	£57,554	£79,000	0%
AE costs, LCI	3.570	2.404	£197,564	2.797	1.841	£153,317	0.773	0.563	£44,247	£57,261	£78,598	-1%
AE costs, UCI	3.570	2.404	£198,356	2.797	1.841	£153,576	0.773	0.563	£44,780	£57,951	£79,545	1%
BTZ admin, LCI	3.570	2.404	£195,867	2.797	1.841	£152,021	0.773	0.563	£43,846	£56,742	£77,885	-1%
BTZ admin, UCI	3.570	2.404	£200,425	2.797	1.841	£155,156	0.773	0.563	£45,269	£58,584	£80,414	2%
Monitoring costs, LCI	3.570	2.404	£196,962	2.797	1.841	£152,980	0.773	0.563	£43,982	£56,919	£78,128	-1%
Monitoring costs, UCI	3.570	2.404	£199,097	2.797	1.841	£153,991	0.773	0.563	£45,107	£58,374	£80,125	1%

* for all base case models (eg. all PFS models), regression parameters are set to the lower / upper 95% CI boundary (eg. shape and scale parameters at the same time)

AE, adverse events; BSC, best supportive care; BTZ, bortezomib; c, cycle; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LCI, 95% lower confidence interval; LEN, lenalidomide; LOT, line of treatment; LYs, life years; off-Tx, off treatment; PANO, panobinostat; PFS, progression-free survival; QALYs, quality-adjusted life years; Tx, treatment; UCI, 95% upper confidence interval.

5.8.3 Scenario analysis

Scenario analyses were conducted around assumptions in the model and are presented in Table 70.

Table 70 Scenario analyses conducted with base values and scenario values

Parameter	Base Value	Scenario Value
Use documented dose intensity (PANORAMA-1)	Yes	No
Discount rate	3.5%	5%
Time Horizon	25 years	5 years, 10 years
PFS (PANO/BTZ/DEX, BTZ/DEX responders)	Weibull (ITT)	Kaplan–Meier + best fitting model Loglogistic Lognormal Gompertz Exponential
Proportion of progressors in PFS (PANO/BTZ/DEX, BTZ/DEX responders)	Logistic regression	Raw trial data
Time to discontinuation (PANO/BTZ/DEX, BTZ/DEX responders	Loglogistic model	Kaplan–Meier estimates

Notes: 'Kaplan–Meier + best fitting model' refers to a model that uses the Kaplan–Meier estimate until the maximum follow-up time and the best fitting model beyond the maximum follow-up time.
BTZ, bortezomib; DEX, dexamethasone; ITT, Intention-to-treat; PANO, panobinostat; PFS, progression-free survival

Modelling PFS with other parametric functions than the Weibull function (as done in the base case model) provides lower ICERs in all cases, which might indicate that the health economic model is conservative in terms of ICER predictions. Ignoring dose reductions as observed in the PANORAMA-1 trial leads to a higher ICER than in the base case model. This is because the total costs increase more for PANO/BTZ/DEX than the total costs increase for BTZ/DEX (1. the dose intensity for panobinostat increases from 80.7% as observed in the trial to 100%; 2. the dose intensity for both bortezomib and dexamethasone were lower in the PANO/BTZ/DEX combination treatment than in the BTZ/DEX combination treatment). Shorter time horizon results in lower incremental QALYs and lower incremental cost compared to the base case results, which ultimately yields more favourable ICERs, especially at a 5-year model time span. The use of rebate for BTZ+DEX impacts the results although only to a limited extent. Different treatment patterns after eight cycles of BTZ/DEX treatment may influence the results significantly. The more patients continue without treatment, the worse the ICER is. In contrast, the more patients continue with LEN/DEX treatment, the better the ICER is. Other scenarios did not impact the ICER substantially.

Table 71 Scenario analyses results

Base case: assuming £776 per 20 mg capsule

	PANO/BTZ/DEX			BTZ/DEX			Incremental			ICER		
	LYs	QALYs	Costs	LYs	QALYs	Costs	LYs	QALYs	Costs	£/LY	£/QALY	change to £/QALY
PFS												
Loglogistic PFS	3.923	2.675	£197,418	2.838	1.870	£154,925	1.084	0.805	£42,493	£39,187	£52,774	-33%
Lognormal PFS	3.862	2.631	£195,583	2.781	1.830	£151,992	1.081	0.801	£43,591	£40,336	£54,433	-31%
Gompertz PFS	3.511	2.365	£194,495	2.723	1.790	£150,027	0.788	0.575	£44,468	£56,432	£77,299	-2%
Exponential PFS	3.563	2.411	£191,119	2.633	1.728	£145,748	0.930	0.684	£45,371	£48,760	£66,374	-16%
KM + best fitting curve	3.610	2.432	£199,126	2.817	1.854	£154,420	0.793	0.578	£44,706	£56,364	£77,308	-2%
Proportion of progressors in PFS												
Raw trial data based	3.537	2.383	£195,886	2.805	1.846	£153,794	0.732	0.537	£42,092	£57,479	£78,372	-1%
Discontinuation												
Raw trial data based	3.570	2.404	£197,705	2.798	1.841	£153,680	0.772	0.563	£44,026	£57,021	£78,197	-1%
Time horizon												
Time horizon 5 years	2.907	1.979	£151,743	2.361	1.562	£121,542	0.545	0.417	£30,201	£55,385	£72,438	-8%
Time horizon 10 years	3.462	2.334	£189,456	2.727	1.795	£147,864	0.735	0.539	£41,592	£56,569	£77,171	-2%
Discount rate												
Discount rate: 5%	3.421	2.306	£189,058	2.693	1.774	£146,816	0.728	0.533	£42,242	£58,037	£79,297	0%
Rebate for BTZ/DEX												
Yes	3.570	2.404	£197,922	2.797	1.841	£150,111	0.773	0.563	£47,811	£61,873	£84,929	7%
Treatment pattern after 8 cycles (BTZ/DEX, Off-Tx, LEN/DEX)												
33% - 33% - 33%	3.570	2.404	£197,922	2.852	1.877	£156,202	0.718	0.526	£41,720	£58,122	£79,298	0%
100% - 0% - 0%	3.570	2.404	£197,922	3.009	1.986	£162,301	0.561	0.417	£35,621	£63,503	£85,370	8%
0% - 100% - 0%	3.570	2.404	£197,922	2.772	1.836	£146,170	0.798	0.567	£51,751	£64,891	£91,203	15%
0% - 0% - 100%	3.570	2.404	£197,922	2.775	1.810	£160,123	0.795	0.593	£37,798	£47,562	£63,693	-19%
Distribution of LLoT (POM/DEX, Other active treatment, BSC)												
33% - 33% - 33%	3.570	2.404	£197,687	2.797	1.841	£153,214	0.773	0.563	£44,473	£57,554	£79,000	0%

100% - 0% - 0%	3.570	2.404	£277,547	2.797	1.841	£228,195	0.773	0.563	£49,352	£63,868	£87,667	11%
0% - 100% - 0%	3.570	2.404	£168,407	2.797	1.841	£125,723	0.773	0.563	£42,684	£55,239	£75,822	-4%
0% - 0% - 100%	3.570	2.404	£147,257	2.797	1.841	£105,865	0.773	0.563	£41,392	£53,566	£73,527	-7%
Utility Off treatment												
Measured at screening	3.570	2.408	£197,922	2.797	1.842	£153,434	0.773	0.566	£44,487	£57,572	£78,606	-1%

BSC, best supportive care; BTZ, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; KM, Kaplan–Meier; LEN, lenalidomide; LYs, life years; off-Tx, off treatment; PANO, panobinostat; PFS, progression-free survival; POM, pomalidomide; QALYs, quality-adjusted life years

5.8.4 Summary of sensitivity analyses results

The mean ICER using probabilistic analysis was similar to the deterministic ICER. 0% of probabilistic results observations were cost-effective at a £30,000 per QALY threshold.

The most influential parameters in the model are the parametric form and the regression parameters for the modelled PFS, the proportion of who progress, treatment discontinuation rates and the risk of progression in patients who are off treatment at the end of cycle 8. The model is structurally sensitive to the treatment pathway parameters (ie. the proportion of patients who continue bortezomib, go off treatment, initiate LEN/DEX treatment) after eight BTZ/DEX treatment cycles.

For the majority of potential inputs PANO/BTZ/DEX remains within the same range of cost-effectiveness estimates when compared to BTZ/DEX treatment.

5.9 Subgroup analysis

See Appendix 17 for subgroup analysis for patients who received a prior IMiD, bortezomib and had two prior lines of treatment.

5.10 Validation

5.10.1 Validation of de novo cost-effectiveness analysis

Consistency with previous appraisals of multiple myeloma and published literature

Expert validation

Excel formulas, model logic and input data were verified for accuracy as part of quality-control procedures by an experienced modeller not involved in the model development. Notably, excel formulas were checked to ensure they reflect the logic of the model. In addition, the model was varied within extreme value beyond what would be considered “reasonable” to ascertain whether the change in the simulated costs and utilities was consistent with a priori expectation. Model predictions were also compared to observed data when possible.

Comparability with UK population

Quality Control

Finally, the model was also quality-assured by internal processes at the company who built the economic model. In these processes, an economist not involved in the model’s construction reviewed the model for coding errors, inconsistencies and the plausibility of inputs.

5.11 Interpretation and conclusions of economic evidence

Strength

Model's flexibility: The model incorporates numerous flexibilities, which allows for testing of assumptions and alternative scenarios. Of note, the model is flexible to allow different options (ie different parametric functions) for projecting PFS. This again allows for alternative assumptions to be tested and the impact of each parametric fit to be observed.

Modelling approach and structure: The model, aiming to reflect the local clinical practice for treatment of relapsed or refractory MM patients, is a treatment sequencing model that allows health economic evidence generation for the UK in the absence of observed trial data for all the clinical pathways. Finally, the modelling approach was based on a thorough review of published economic modelling approaches and available HTA submission reports. Review of these existing modelling approaches and of the available criticism allowed our analysis to adopt best practices and account for or address aspects of models that have been critiqued in the past.

Use of patient level data: To a large extent the model was informed by data from the pivotal PANORAMA-1 trial. Individual patient level data was available to derive most input parameters. The trial included 768 patients thus for several model parameters robust estimates could be obtained that in turn also reflected in the model results.

Limitations

The key limitation of the economic model was that PFS and OS data had to be extrapolated given neither PFS nor OS is fully captured (not all patients experienced a corresponding event) in the PANORAMA 1 trial. Nonetheless, by using PFS and OS data from the trial itself the best available evidence to date have been used. Extrapolation of PFS using different parametric distributions showed that the model outcomes were sensitive to the use of different parametric models.

Despite the fact that various particular treatment decision rules specific to the UK (ie, treatment continuation decision per PAS based on response at the end of the fourth cycle; treatment continuation decision per bortezomib license at the eighth cycle) were not applied in the PANORAMA-1 trial, for modelling purposes UK clinical practice had to be taken into account. As a consequence assumptions had to be made on some of the input data for the control arm of the model. Efforts have been made to choose these input data such that they reflect clinical reality.

Utility values specific to relapsed or relapsed and refractory MM were not available in the literature. Therefore, an analysis was conducted to map QLQ-C30 data collected in PANORAMA 1 trial to EQ-5D values by using a published mapping algorithm. This allowed MM-specific utility values to be derived for the treatment arms. However, it was not possible to derive utility values associated with

the off-treatment and with later treatment lines using the mapping method. Therefore, the model relies on utility values that were obtained from the literature.

Conclusions

Based on the available data, the current analyses indicate that PANO/BTZ/DEX is an effective treatment for relapsed or relapsed and refractory MM, offering prolonged PFS, treatment-free phase and OS versus BTZ/DEX. Given the model's sensitivity to the drug price, the cost-effectiveness of the PANO/BTZ/DEX triple combination will depend on its final cost.

6 Assessment of factors relevant to the NHS and other parties

Given the disease characteristics for budget impact calculation purposed incidence rate was used only. The incidence of MM is estimated to be 5.4/100.000[20]. Based on a population of 56,948,200[21] and at a growth rate of 0.677%[22], this would suggest that there were 3117 patients diagnosed with MM in England and Wales in 2015.

The following assumptions were made to derive the eligible patient pool in second-line use.

- 70.4%[23] receives chemotherapy, while the remainder 29.6% remain on active monitoring or receives radiotherapy, supportive care, palliative care or treated for non-haematological comorbidities only.
- 86.5%[24] of patients survive to receive second-line treatment, derived from the proportion of patients surviving at the mean time to progression (1.04 years) for VMT.
- 71% of the patients who receive an IMiD in first line or SCT in first line receives bortezomib in second line. As panobinostat is an add-on treatment to BTZ/DEX, we assume the full eligible patient number equal to that.
- Given the uncertainties around the final label and the possible restrictions we are assuming those, who would receive BTZ/DEX otherwise were eligible to panobinostat.

[20] Cancer Research UK, UK Cancer Incidence 2011 and Mortality 2012 Summary - Rates, September 2014

[21] http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/2013/index.html

[22] Office of national statistics

[23] HMRN MM audit

[24] The NICE costing template for bortezomib in combination with melphalan and prednisolone (VMT)

Number of patients with MM in England and Wales

	2015	2016	2017	2018	2019
Population of England and Wales	57,721,574	58,112,191	58,505,451	58,901,372	59,299,973
Incidence: 5.4/100,000	3,117	3,138	3,159	3,181	3,202
Treatment rate is 70.4%	2194	2209	2224	2239	2254
86.5% receives any second line treatment	1898	1911	1924	1937	1950
BTZ use in second line following prior IMiD or SCT is 71%	1348	1357	1366	1375	1385

BTZ, bortezomib; MM, multiple myeloma; SCT, stem cell transplantation.

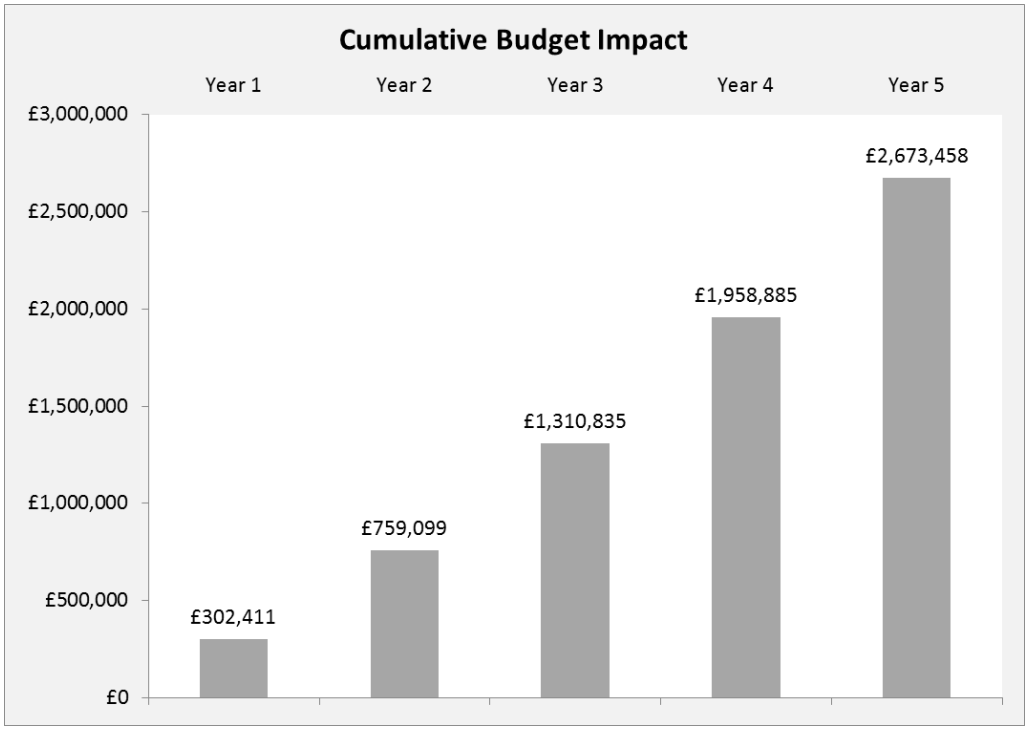
The market uptake of panobinostat is estimated to take the following course:

- • Year 1: 10%
- • Year 2: 15%
- • Year 3: 18%
- • Year 4: 21%
- • Year 5: 23%

Unit costs, as well as costs related to monitoring, administration and adverse event management are based on the costs used in the cost effectiveness model and described in section 5.5.2.

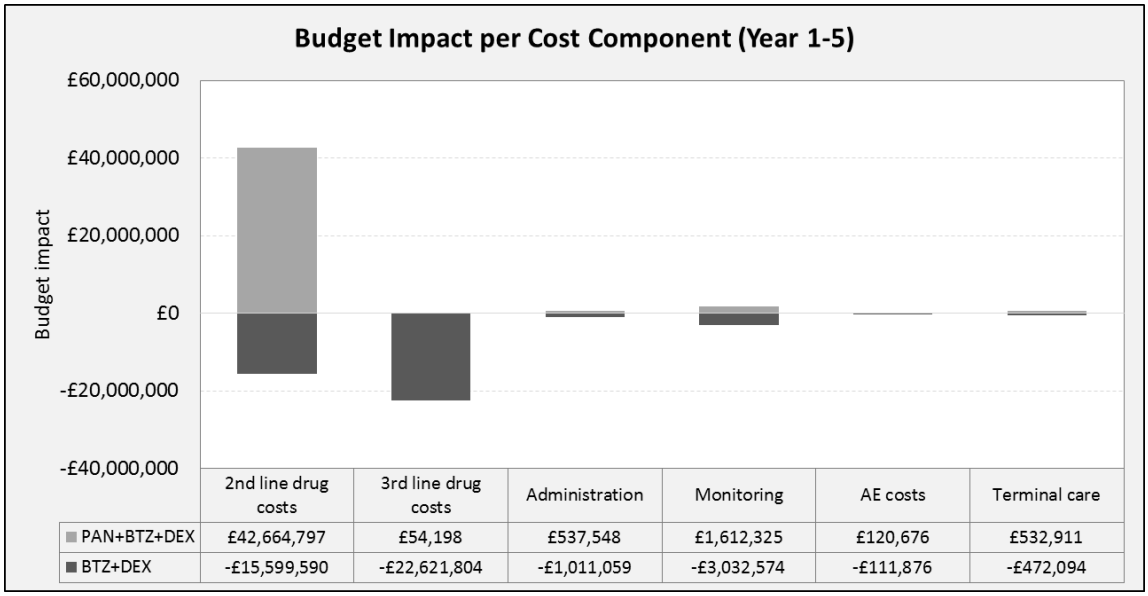
The calculated budget impact per year and the cumulative figures are presented below.

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
PAN/BTZ/DEX	£5,149,326	£7,776,280	£9,394,710	£11,034,698	£12,167,441	£45,522,455
BTZ/DEX	-£4,846,914	-£7,319,592	-£8,842,975	-£10,386,648	-£11,452,868	-£42,848,997
Total per year	£302,411	£456,688	£551,736	£648,050	£714,574	£2,673,458
%	0.88%	1.32%	1.58%	1.85%	2.02%	1.53%
Cumulative budget impact	£302,411	£759,099	£1,310,835	£1,958,885	£2,673,458	



Total budget impact by cost component is described below.

	2nd line drug costs	3rd line drug costs	Administration	Monitoring	AE costs	Terminal care	Total
PAN/BTZ/DEX	£42,664,797	£54,198	£537,548	£1,612,325	£120,676	£532,911	£45,522,455
BTZ/DEX	-£15,599,590	-£22,621,804	-£1,011,059	-£3,032,574	-£111,876	-£472,094	-£42,848,997
GRAND TOTAL	£27,065,206	-£22,567,605	-£473,511	-£1,420,250	£8,801	£60,817	£2,673,458



There may be wider societal benefits due to the longer TFI associated to panobinostat which have not been included in the above resource impact estimation.

7 References

1. Ververis K, Hiong A, Karagiannis TC, Licciardi PV. Histone deacetylase inhibitors (HDACIs): multitargeted anticancer agents. *Biologics* 2013;7:47–60.
2. Dimopoulos K, Gimsing P, Gronbaek K. The role of epigenetics in the biology of multiple myeloma. *Blood Cancer J* 2014;4:e207.
3. Maes K, Menu E, Van Valckenborgh E *et al.* Epigenetic modulating agents as a new therapeutic approach in multiple myeloma. *Cancers* 2013;5:430–61. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3730337/pdf/cancers-05-00430.pdf
4. Dokmanovic M, Clarke C, Marks PA. Histone deacetylase inhibitors: overview and perspectives. *Mol Cancer Res* 2007;5:981–9.
5. Hideshima T, Bradner JE, Wong J *et al.* Small-molecule inhibition of proteasome and aggresome function induces synergistic antitumor activity in multiple myeloma. *Proc Natl Acad Sci U S A* 2005;102:8567–72.
6. Atadja P. Development of the pan-DAC inhibitor panobinostat (LBH589): successes and challenges. *Cancer Lett* 2009;280:233–41.
7. Simms-Waldrip T, Rodriguez-Gonzalez A, Lin T *et al.* The aggresome pathway as a target for therapy in hematologic malignancies. *Mol Genet Metab* 2008;94:283–6.
8. Ocio EM, Vilanova D, Atadja P *et al.* In vitro and in vivo rationale for the triple combination of panobinostat (LBH589) and dexamethasone with either bortezomib or lenalidomide in multiple myeloma. *Haematologica* 2010;95:794–803. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2864386/pdf/0950794.pdf
9. San-Miguel JF, Hungria VT, Yoon SS *et al.* Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. *Lancet Oncol* 2014;15:1195–206.
10. Richardson PG, Schlossman RL, Alsina M *et al.* PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. *Blood* 2013;122:2331–7.
11. San-Miguel JF, Richardson PG, Gunther A *et al.* Phase Ib study of panobinostat and bortezomib in relapsed or relapsed and refractory multiple myeloma. *J Clin Oncol* 2013;31:3696–703.
12. Richardson PG, Sonneveld P, Schuster M *et al.* Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. *Blood* 2007;110 3557–60.
13. Moreau P, Pylypenko H, Grosicki S *et al.* Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *Lancet Oncol* 2011;12 431–40.

14. Kumar SK, Lee JH, Lahuerta JJ *et al.* Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. *Leukemia* 2012;26:149–57.
15. Arnulf B, Pylypenko H, Grosicki S *et al.* Updated survival analysis of a randomized phase III study of subcutaneous versus intravenous bortezomib in patients with relapsed multiple myeloma. *Haematologica* 2012;97:1925–8. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3685287/pdf/0971925.pdf
16. Palumbo A, Cavallo F. Have drug combinations supplanted stem cell transplantation in myeloma? *Blood* 2012;120:4692–8.
17. Chanan-Khan AA, Giralt S. Importance of achieving a complete response in multiple myeloma, and the impact of novel agents. *J Clin Oncol* 2010;28:2612–24.
18. Oncologic Drugs Advisory Committee (ODAC). PANORAMA-1 landmark analysis; ODAC report
19. Niesvizky R, Richardson PG, Rajkumar SV *et al.* The relationship between quality of response and clinical benefit for patients treated on the bortezomib arm of the international, randomized, phase 3 APEX trial in relapsed multiple myeloma. *Br J Haematol* 2008;143:46–53.
20. Richardson PG, Sonneveld P, Schuster MW *et al.* Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2005;352:2487–98.
21. Orlowski RZ, Nagler A, Sonneveld P *et al.* Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. *J Clin Oncol* 2007;25:3892–901.
22. Dimopoulos M, Siegel DS, Lonial S *et al.* Vorinostat or placebo in combination with bortezomib in patients with multiple myeloma (VANTAGE 088): a multicentre, randomised, double-blind study. *Lancet Oncol* 2013;14:1129–40.
23. Acaster S, Gaugris S, Velikova G, Yong K, Lloyd AJ. Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: a UK cross-sectional survey. *Support Care Cancer* 2013;21:599–607.
24. Richardson D, Schlossman R, Alsina M *et al.* 2013. Time To Event Analyses in PANORAMA 2: A Phase 2 Study Of Panobinostat, Bortezomib, and Dexamethasone In Patients With Relapsed and Bortezomib-Refractory Multiple Myeloma 55th ASH Annual Meeting and Exhibition. New Orleans, LA, USA.
25. Food & Drug Administration. FDA Briefing Document Oncologic Drugs Advisory Committee Meeting, 6 November 2014.NDA 205353 panobinostat (Farydak) Novartis. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM421623.pdf. (Accessed 30 January 2015).
26. Moreau P, Coiteux V, Hulin C *et al.* Prospective comparison of subcutaneous versus intravenous administration of bortezomib in patients with multiple myeloma. *Haematologica* 2008;93:1908–11. http://www.haematologica.org/content/93/12/1908.full-text.pdf+html

27. Bringhen S, Larocca A, Rossi D *et al.* Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. *Blood* 2010;116:4745–53.
28. Farydak (panobinostat). Draft summary of product characteristics.
29. Catley L, Weisberg E, Kiziltepe T *et al.* Aggresome induction by proteasome inhibitor bortezomib and alpha-tubulin hyperacetylation by tubulin deacetylase (TDAC) inhibitor LBH589 are synergistic in myeloma cells. *Blood* 2006;108:3441–9.
30. Mitsiades N, Mitsiades CS, Richardson PG *et al.* Molecular sequelae of histone deacetylase inhibition in human malignant B cells. *Blood* 2003;101:4055-62.
31. Bali P, Pranpat M, Bradner J *et al.* Inhibition of histone deacetylase 6 acetylates and disrupts the chaperone function of heat shock protein 90: a novel basis for antileukemia activity of histone deacetylase inhibitors. *J Biol Chem* 2005;280:26729–34.
32. Hideshima T, Richardson PG, Anderson KC. Mechanism of action of proteasome inhibitors and deacetylase inhibitors and the biological basis of synergy in multiple myeloma. *Mol Cancer Ther* 2011;10:2034–42.
33. Obeng EA, Carlson LM, Gutman DM *et al.* Proteasome inhibitors induce a terminal unfolded protein response in multiple myeloma cells. *Blood* 2006;107:4907–16.
34. San Miguel JF, Schlag R, Khuageva NK *et al.* Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med* 2008;359:906–17.
35. Farydak (panobinostat). Patient Information. Available from: http://www.pharma.us.novartis.com/product/pi/pdf/farydak.pdf. (Accessed 5 May 2015).
36. Maiso P, Carvajal-Vergara X, Ocio EM *et al.* The histone deacetylase inhibitor LBH589 is a potent antimyeloma agent that overcomes drug resistance. *Cancer Res* 2006;66:5781–9.
37. Kuehl WM, Bergsagel PL. Molecular pathogenesis of multiple myeloma and its premalignant precursor. *J Clin Invest* 2012;122:3456–63.
38. Lawasut P, Groen RW, Dhimolea E *et al.* Decoding the pathophysiology and the genetics of multiple myeloma to identify new therapeutic targets. *Semin Oncol* 2013;40:537–48.
39. Borrello I. Can we change the disease biology of multiple myeloma? *Leuk Res* 2012;36 Suppl 1:S3–12.
40. Chesi M, Bergsagel PL. Molecular pathogenesis of multiple myeloma: basic and clinical updates. *Int J Hematol* 2013;97:313–23.
41. Jagannath S. Pathophysiological underpinnings of multiple myeloma progression. *J Manag Care Pharm* 2008;14:7–11. http://www.amcp.org/data/jmcp/Sept08%20Suppl_S7-S11.pdf
42. Katzel JA, Hari P, Vesole DH. Multiple myeloma: charging toward a bright future. *CA Cancer J Clin* 2007;57:301–18.
43. Laubach J, Richardson P, Anderson K. Multiple myeloma. *Annu Rev Med* 2011;62:249–64.
44. Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med* 2011;364:1046–60.
45. Raab MS, Podar K, Breitkreutz I, Richardson PG, Anderson KC. Multiple myeloma. *Lancet* 2009;374:324–39.
46. CancerMPact® Western Europe. Treatment architecture: Western Europe multiple myeloma. 2013.

47. Kumar SK, Therneau TM, Gertz MA *et al.* Clinical course of patients with relapsed multiple myeloma. *Mayo Clin Proc* 2004;79:867–74.
48. Laubach JP, Voorhees PM, Hassoun H *et al.* Current strategies for treatment of relapsed/refractory multiple myeloma. *Expert Rev Hematol* 2014;7:97–111.
49. Kumar SK, Rajkumar SV, Dispenzieri A *et al.* Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 2008;111:2516–20.
50. Durie BG, Kyle RA, Belch A *et al.* Myeloma management guidelines: a consensus report from the Scientific Advisors of the International Myeloma Foundation. *Hematol J* 2003;4:379–98.
51. Bird JM, Owen RG, D'Sa S *et al.* Guidelines for the diagnosis and management of multiple myeloma 2014. Available from: http://www.bcshguidelines.com/documents/MYELOMA_GUIDELINE_Feb_2014_for_BCSH.pdf. (Accessed 4 June 2014).
52. National Institute for Health and Care Excellence. Technology Appraisal 228: Bortezomib and thalidomide for the first-line treatment of multiple myeloma. July 2011. Available from: https://www.nice.org.uk/guidance/ta228 (Accessed 5 June 2014).
53. Zaidi AA, Vesole DH. Multiple myeloma: an old disease with new hope for the future. *CA Cancer J Clin* 2001;51:273–85; quiz 286–9.
54. Gay F, Palumbo A. Management of disease- and treatment-related complications in patients with multiple myeloma. *Med Oncol* 2010;27 (Suppl 1):S43–52.
55. Richardson PG, Delforge M, Beksac M *et al.* Management of treatment-emergent peripheral neuropathy in multiple myeloma. *Leukemia* 2012;26:595–608.
56. Snowden JA, Ahmedzai SH, Ashcroft J *et al.* Guidelines for supportive care in multiple myeloma 2011. *Br J Haematol* 2011;154:76–103.
57. Palumbo A, Mina R. Management of older adults with multiple myeloma. *Blood Rev* 2013;27:133–42.
58. Ludwig H, Durie BG, Bolejack V *et al.* Myeloma in patients younger than age 50 years presents with more favorable features and shows better survival: an analysis of 10 549 patients from the International Myeloma Working Group. *Blood* 2008;111:4039–47.
59. Lonial S. Presentation and risk stratification--improving prognosis for patients with multiple myeloma. *Cancer Treat Rev* 2010;36 (Suppl 2):S12–7.
60. Haematological Malignancy Research Network. Clinical management and outcome of myeloma. Version 3.0.
61. Ghatnekar O, Alvegard T, Conradi N *et al.* Direct hospital resource utilization and costs of treating patients with multiple myeloma in Southwest Sweden: a 5-year retrospective analysis. *Clin Ther* 2008;30:1704–13.
62. Melton LJ, 3rd, Kyle RA, Achenbach SJ, Oberg AL, Rajkumar SV. Fracture risk with multiple myeloma: a population-based study. *J Bone Miner Res* 2005;20:487–93.
63. Kleber M, Ihorst G, Gross B *et al.* Validation of the Freiburg Comorbidity Index in 466 multiple myeloma patients and combination with the international staging system are highly predictive for outcome. *Clin Lymphoma Myeloma Leuk* 2013;13:541–51.

64. Strasser-Weippl K, Ludwig H. Psychosocial QOL is an independent predictor of overall survival in newly diagnosed patients with multiple myeloma. *Eur J Haematol* 2008;81:374–9.
65. Petrucci MT, Calabrese E, Levi A *et al.* Costs and quality of life of multiple myeloma (MM) in Italy: the CO.MI.M study. *Value Health* 2009;12:A265.
66. Johnsen AT, Tholstrup D, Petersen MA, Pedersen L, Groenvold M. Health related quality of life in a nationally representative sample of haematological patients. *Eur J Haematol* 2009;83:139–48.
67. Jordan K, Proskorovsky I, Lewis P *et al.* Effect of general symptom level, specific adverse events, treatment patterns, and patient characteristics on health-related quality of life in patients with multiple myeloma: results of a European, multicenter cohort study. *Support Care Cancer* 2014;22:417–26.
68. Molassiotis A, Wilson B, Blair S, Howe T, Cavet J. Unmet supportive care needs, psychological well-being and quality of life in patients living with multiple myeloma and their partners. *Psychooncology* 2011;20:88–97.
69. Molassiotis A, Wilson B, Blair S, Howe T, Cavet J. Living with multiple myeloma: experiences of patients and their informal caregivers. *Support Care Cancer* 2011;19:101–11.
70. Lobban R, Myeloma UK, Schey S. Living with myeloma-related pain: perceptions of UK patients, careers and consultants. *Haematologica* 2012;97 (Suppl 1):444. http://www.haematologica.org/content/97/supplement_1/haematol_97_s1.full.pdf+html?
71. Ludwig H, Miguel JS, Dimopoulos MA *et al.* International Myeloma Working Group recommendations for global myeloma care. *Leukemia* 2014;28:981–92.
72. Moreau P, San Miguel J, Ludwig H *et al.* Multiple myeloma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24 (Suppl 6):133–7.
73. Engelhardt M, Terpos E, Kleber M *et al.* European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. *Haematologica* 2014;99:232–42. http://www.haematologica.org/content/99/2/232.long
74. Palumbo A, Rajkumar SV, San Miguel JF *et al.* International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. *J Clin Oncol* 2014;32:587–600.
75. mSMART (Mayo Stratification for Myeloma And Risk-adapted Therapy). Relapsed myeloma. v1 Jan 2008. Last reviewed September 2012.
76. Rajkumar SV. Multiple myeloma: 2013 update on diagnosis, risk-stratification, and management. *Am J Hematol* 2013;88:226–35.
77. Rajkumar SV. Treatment of multiple myeloma. *Nat Rev Clin Oncol* 2011;8:479–91.
78. Anderson KC, Alsina M, Bensinger W *et al.* Multiple myeloma, version 1.2013. *J Natl Compr Canc Netw* 2013;11:11–7.
79. National Chemotherapy Algorithms. Multiple myeloma. Available from: https://www.engage.england.nhs.uk/consultation/specialised-services-consultation/user_uploads/chemothrpy-algrthms-mltpl-myeloma.pdf ; (Accessed 8 May 2015).

80. Kumar SK, Dispenzieri A, Lacy MQ *et al.* Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia* 2014;28:1122–8.
81. Liwing J, Uttervall K, Lund J *et al.* Improved survival in myeloma patients: starting to close in on the gap between elderly patients and a matched normal population. *Br J Haematol* 2014;164:684–93.
82. Cancer Research UK. Myeloma statistics. Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/myeloma/uk-multiple-myeloma-statistics. (Accessed November 2014).
83. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64:9–29.
84. Cancer Research UK. Myeloma survival statistics. Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/myeloma/survival/. (Accessed 17 June 2014).
85. National Institute for Health and Care Excellence. Technology Appraisal 311: Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation. April 2014. Available from: https://www.nice.org.uk/guidance/ta311 (Accessed 5 June 2014).
86. National Institute for Health and Care Excellence. NICE clinical guideline wave 0669.
87. National Institute for Health and Care Excellence. Technology Appraisal 171: Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. June 2009. Available from: http://www.nice.org.uk/TA171. (Accessed 4 October 2013).
88. National Institute for Health and Care Excellence. Technology Appraisal 129: Bortezomib monotherapy for relapsed multiple myeloma. October 2007. Available from: www.nice.org.uk/TA129. (Accessed 4 October 2013).
89. National Cancer Drugs Fund List. Version 4.0. 12 March 2015. Available from: http://www.england.nhs.uk/wp-content/uploads/2015/03/ncdf-list-mar-15.pdf (Accessed 14 April 2015).
90. National Institute for Health and Care Excellence. Technology Appraisal 311: Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation. April 2014. Available from: www.nice.org.uk/TA311 (Accessed 4 October 2013).
91. National Institute for Health and Care Excellence. NICE issues preliminary guidance on pomalidomide for blood cancer, 15 October 2014. Available from: https://www.nice.org.uk/news/press-and-media/nice-issues-preliminary-guidance-on-pomalidomide-for-blood-cancer. (Accessed 10 November 2014).
92. Data on file. TWiST analysis ODAC 2014
93. Dimopoulos MA, Chen C, Spencer A *et al.* Long-term follow-up on overall survival from the MM–009 and MM–010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. *Leukemia* 2009;23 2147–52.

94. San Miguel J, Weisel K, Moreau P *et al.* Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *The lancet oncology* 2013;14:1055–66.
95. Dimopoulos M, Spencer A, Attal M *et al.* Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 2007;357 2123–32.
96. Lonial S, Anderson KC. Association of response endpoints with survival outcomes in multiple myeloma. *Leukemia* 2014;28:258–68.
97. San-Miguel J, Hungria VTM, Yoon S-S *et al.* Efficacy and safety based on duration of treatment of panobinostat plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma in the phase 3 Panorama 1 study. *Blood* 2014;124:4742.
98. San-Miguel JF, Hungria VT, Yoon SS *et al.* Correction to Lancet Oncol 2014; 15: 1195–206. *Lancet Oncol* 2015;16:e6.
99. Bengoudifa B, Sopala M, Lin R *et al.* Full Clinical Study Report: Panobinostat/LBH589 A multicenter, randomized, double-blind, placebo-controlled phase III study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma.
100. Richardson PG, Hungria VTM, Yoon SB, M. *et al.* PANORAMA 1: a randomized, double-blind, phase 3 study of panobinostat or placebo plus bortezomib and dexamethasone in relapsed or relapsed and refractory multiple myeloma. Podium presentation presentated at the American Society of Clinical Oncology (ASCO) Annual Meeting, 30 May – 3 June 2014, Chicago, Illinois
101. Richardson P, Alsina M, Weber D *et al.* PANORAMA 2: a phase II study of panbinostat in combination with bortezomib and dexamethasone in patients with relpsed and bortezomib-refractory multiple myeloma *Haematologica* 2012;97 (Suppl 1):827. http://www.haematologica.org/content/haematol/97/supplement_1/haematol_97_s1.full.pdf
102. Blade J, Samson D, Reece D *et al.* Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *Br J Haematol* 1998;102:1115–23.
103. Richardson PG, Barlogie B, Berenson J *et al.* A phase 2 study of bortezomib in relapsed, refractory myeloma. *N Engl J Med* 2003;348:2609–17.
104. Durie BG, Harousseau JL, Miguel JS *et al.* International uniform response criteria for multiple myeloma. *Leukemia* 2006;20:1467–73.
105. Novartis. Data on file. Interim CSR.
106. Celgene. Revlimid (lenalidomide) Summary of product characteristics. Available from: https://www.medicines.org.uk/emc/medicine/19841; (Accessed 8 May 2015).
107. Siegel D, Richardson D, Dimopoulos K, al e. Efficacy and safety of pomalidomide plus low-dose dexamethasone in advanced multiple myeloma: results of randomized phase 2 and 3 trials (MM-002/MM-003) Abstract presented at American Society of Hematology annual

meeting, New Orleans, LA , USA, 7-10 December 2013; Abstract 3185. http://www.bloodjournal.org/content/122/21/3185?sso-checked=true

108. Lee SJ, Richardson PG, Sonneveld P *et al.* Bortezomib is associated with better health-related quality of life than high-dose dexamethasone in patients with relapsed multiple myeloma: results from the APEX study. *Br J Haematol* 2008;143:511–9.
109. Richardson PG, Lee JH, Majer I, Krishna A, Woodman RC. Efficacy of treatments in relapsed or relapsed and refractory multiple myeloma: an indirect treatment comparison. Abstract submitted to the 56th ASH Annual Meeting and Exposition 6–9 December 2014, San Francisco, California, USA.
110. Hjorth M, Hjertner O, Knudsen LM *et al.* Thalidomide and dexamethasone vs. bortezomib and dexamethasone for melphalan refractory myeloma: a randomized study. *Eur J Haematol* 2012;88 485–96.
111. Garderet L, Iacobelli S, Moreau P *et al.* Superiority of the triple combination of bortezomib-thalidomide-dexamethasone over the dual combination of thalidomide-dexamethasone in patients with multiple myeloma progressing or relapsing after autologous transplantation: the MMVAR/IFM 2005-04 Randomized Phase III Trial from the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol* 2012;30:2475–82.
112. Dimopoulos MA, Chen C, Spencer A *et al.* Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. *Leukemia* 2009;23:2147–52.
113. Weber DM, Chen C, Niesvizky R *et al.* Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med* 2007;357 2133–42.
114. Dimopoulos MA, Orlowski RZ, Facon T *et al.* Retrospective matched-pair analysis of the efficacy and safety Of bortezomib plus dexamethasone versus bortezomib monotherapy in patients (Pts) with relapsed multiple myeloma (MM). Poster presented at the 55th ASH Annual Meeting and Exposition, 7–10 December 2013, New Orleans, Louisiana, USA.
115. Dimopoulos MA, Hamilos G, Zomas A *et al.* Pulsed cyclophosphamide, thalidomide and dexamethasone: an oral regimen for previously treated patients with multiple myeloma. *Hematol J* 2004;5 112–7.
116. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;50:683–91.
117. Spiegelhalter DJ, Best NG. Bayesian approaches to multiple sources of evidence and uncertainty in complex cost-effectiveness modelling. *Stat Med* 2003;22:3687–709.
118. Signorovitch J, Swallow E, Kantor E *et al.* Everolimus and sunitinib for advanced pancreatic neuroendocrine tumors: a matching-adjusted indirect comparison. *Exp Hematol Oncol* 2013;2:32.
119. Di Lorenzo G, Casciano R, Malangone E *et al.* An adjusted indirect comparison of everolimus and sorafenib therapy in sunitinib-refractory metastatic renal cell carcinoma patients using repeated matched samples. *Expert Opin Pharmacother* 2011;12:1491–7.

120. Signorovitch JE, Wu EQ, Betts KA *et al.* Comparative efficacy of nilotinib and dasatinib in newly diagnosed chronic myeloid leukemia: a matching-adjusted indirect comparison of randomized trials. *Curr Med Res Opin* 2011;27:1263–71.
121. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;12:9.
122. Signorovitch JE, Wu EQ, Yu AP *et al.* Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. *Pharmacoeconomics* 2010;28:935–45.
123. Richardson PG, Hungria V, Yoon S, al e. Characterization of the incidence and management of gastrointestinal toxicity in the phase 3 Panorama 1 study of panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma. Abstract presented at the 56th Annual Meeting of the American Society of Hematology, San Francisco, CA, December 6, 2014. Abstract 2120.
124. Harousseau JL, Attal M, Avet-Loiseau H. The role of complete response in multiple myeloma. *Blood* 2009;114:3139–46.
125. Pratt G, Jenner M, Owen R *et al.* Updates to the guidelines for the diagnosis and management of multiple myeloma. *Br J Haematol* 2014;167:131–3.
126. Green C, Bryant J, Takeda A *et al.* Bortezomib for the treatment of multiple myeloma patients. *Health Technol Assess* 2009;13 (Suppl 1):29–33.
127. Hornberger J, Rickert J, Dhawan R *et al.* The cost-effectiveness of bortezomib in relapsed/refractory multiple myeloma: Swedish perspective. *Eur J Haematol* 2010;85 484–91.
128. Moller J, Nicklasson L, Murthy A. Cost-effectiveness of novel relapsed-refractory multiple myeloma therapies in Norway: lenalidomide plus dexamethasone vs bortezomib. *J Med Econ* 2011;14 690–7.
129. Brown RE, Stern S, Dhanasiri S, Schey S. Lenalidomide for multiple myeloma: cost-effectiveness in patients with one prior therapy in England and Wales. *Eur J Health Econ* 2013;14 507–14.
130. Fragoulakis V, Kastritis E, Psaltopoulou T, Maniadakis N. Economic evaluation of therapies for patients suffering from relapsed-refractory multiple myeloma in Greece. *Cancer Manag Res* 2013;5 37–48.
131. Celgene. NICE Single Technology Appraisal (STA) - Pomalidomide for relapsed and refractory multiple myeloma. June 2014.
132. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Available from: http://www.nice.org.uk/article/pmg9/chapter/Foreword (Accessed 12 March 2015).
133. Aaronson NK, Ahmedzai S, Bergman B *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365–76.

134. Versteegh MM, Leunis A, Luime JJ *et al.* Mapping QLQ-C30, HAQ, and MSIS-29 on EQ-5D. *Med Decis Making* 2012;32:554–68.
135. Proskorovsky I, Lewis P, Williams CD *et al.* Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. *Health Qual Life Outcomes* 2014;12:35.
136. Kharroubi S, et al. Use of Bayesian Markov chain monte Carlo methods to estimate EQ-5D utility scores from EORTC QLQ data in Myeloma for use in cost effectiveness analysis. . *HEJC papers.* 2013.
137. Longworth L, Yang Y, Young T *et al.* Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. *Health Technol Assess* 2014;18:1–224.
138. van Agthoven M, Segeren CM, Buijt I *et al.* A cost-utility analysis comparing intensive chemotherapy alone to intensive chemotherapy followed by myeloablative chemotherapy with autologous stem-cell rescue in newly diagnosed patients with stage II/III multiple myeloma; a prospective randomised phase III study. *Eur J Cancer* 2004;40:1159–69.
139. Dubois D, Dhawan R, van de Velde H *et al.* Descriptive and prognostic value of patient-reported outcomes: the bortezomib experience in relapsed and refractory multiple myeloma. *J Clin Oncol* 2006;24 976–82.
140. Kyriakou C, Petrucci MT, Welslau M *et al.* Exploration and quantification of the determinants of baseline health-related quality of life (HRQOL) for patients in relapsed/refractory multiple myeloma. *Haematologica* 2013;98 (Suppl 1):600.
141. Broek I, Murphy P, Petrucci M *et al.* Comparison of patients' and physicians' perceptions of patients' baseline health-related quality of life in relapsed/refractory multiple myeloma. *Haematologica* 2013;98 (Suppl 1):P1080.
142. Pamuk GE, Uyanik MS, Demir M. Assessment of quality of life in Turkish multiple myeloma patients by using EORTCQLQ- C30 and EORTC-QLQ-MY20. *Clin Lymphoma Myeloma Leuk* 2013;13 (Suppl_1):S220–S221.
143. National Audit Office. End of life care. 2008. Available from: http://www.nao.org.uk/wp-content/uploads/2008/11/07081043.pdf (Accessed: 14 January 2014).
144. Mosteller RD. Mosteller body-surface area calculator. Available from: http://www.patient.co.uk/doctor/body-surface-area-calculator-mosteller (Accessed March 2015).
145. Gooding S, Lau I-J, Sheikh M *et al.* Double refractory myeloma: analysis of clinical outcomes and medical-resource utilisation in a single centre *Blood* 2013;122:Abstract 1727.
146. Pomalidomide (Imnovid). Summary of product characteristics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002682/WC500147717.pdf (Accessed March 2015).
147. Claxton K. Exploring uncertainty in cost-effectiveness analysis. *Pharmacoeconomics* 2008;26:781–98.

148. Drummond M, Barbieri M, Cook J *et al.* Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. *Value Health* 2009;12:409–18.

149. Moreau et al. Analysis of outcomes by response for patients with relapsed or relapsed and refractory multiple myeloma in the phase 3 panorama 1 study of panobinostat or placebo plus bortezomib and dexamethasone. Abstract to be presented at the 20th Congress of European Hematology Association (EHA), 11–14 June 2015, Austria, Vienna. Abstract 3302

150. Hungria et al. Analysis of Outcomes Based on Response for Patients With Relapsed or Relapsed and Refractory Multiple Myeloma in the Phase 3 PANORAMA 1 Study. Poster to be presented at the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting, 29 May 29– 2 June 2015, Chicago, Illinois. Poster 8575.

151. San Miguel et al. Panobinostat plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma who received prior bortezomib and IMiDs: A predefined subgroup analysis of PANORAMA 1. Poster to be presented at the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting, 29 May 29– 2 June 2015, Chicago, Illinois. Poster 8526.

152. Hermann Einsele et al. Subgroup analysis by prior treatment among patients with relapsed or relapsed and refractory multiple myeloma in the PANORAMA 1 study of panobinostat or placebo plus bortezomib and dexamethasone, Abstract to be presented at the 20th Congress of European Hematology Association (EHA), 11–14 June 2015, Austria, Vienna. Abstract 3303.

153. Novartis. Data on file. Manufacturer's Response to CHMP D180 List of Outstanding Issues Clinical Questions.

154. Food and Drug Administration. (FDA). Farydak® (panobinostat) capsules. Full prescribing information. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205353s000lbl.pdf. (Accessed May 2015).

155. Stadtmauer EA, Weber DM, Niesvizky R et al. Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma. Eur J Haematol 2009;82:426–32.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy (ID663)

Company evidence submission
Appendix 17

2015

File name	Version	Contains confidential information	Date
		Yes/no	20 May 2015

Instructions for companies

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This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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1 Economic analysis

1.1 Published cost-effectiveness studies

1.1.1 Identification of studies

A systematic review was performed in August 2013 to identify economic evidence relating to second-line therapy of patients with rrMM. Updates to the review were performed on 24 April 2014 and 3 to 9 December 2014. The search aimed to identify cost-utility studies of treatments for rrMM together with cost analysis studies and resource use studies relating to patients with MM for the following interventions: panobinostat, thalidomide, lenalidomide, bortezomib, pomalidomide, carfilzomib and ixazomib. Specific inclusion and exclusion criteria were utilized to identify relevant references. Two analysts independently screened each reference for inclusion based on title and abstract. A third researcher resolved any differences between results. All publications that met entry criteria for the review were obtained as full articles and reassessed against the review criteria. Data from the selected studies were subsequently used to populate predefined summary tables. All data were fully checked by the third analyst. Further details of the methodology for the reviews are provided in Appendix 11.

To be included in this systematic review, references had to meet the inclusion criteria (and none of the exclusion criteria) detailed in Table 1.

Table 1. Eligibility criteria used in the screening

Variable	Inclusion criteria	Exclusion criteria
Populations	Patients with rrMM, receiving treatment with an intervention of interest for CUA studies Patients with MM for cost analysis and resource use studies	CUA where rrMM-specific results cannot be clearly separated from other data
Interventions	Panobinostat Thalidomide Lenalidomide Bortezomib Pomalidomide Carfilzomib Ixazomib	Specific first-line therapies or ASCT
Outcomes	Study must contain at least one of the following: ICERs cost per clinical outcome total QALYs total LYGs total costs costs reported as an outcome	
Study design	Cost utility Cost effectiveness Cost consequence Cost/resource use	Studies with only clinical outcomes
Publication type	Primary paper Abstract HTA review Systematic review Published from March 2013 to April 2014	Published before March 2013 Editorial Review Letter Reference included in original systematic review
Language restrictions	English	Non-English languages

ASCT, autologous stem cell transplantation; CUA, cost–utility analysis; HTA, health technology assessment; ICER, incremental cost effectiveness ratio; LYG, life-years gained; MM, multiple myeloma; QALY, quality-adjusted life-year; rr, relapsed/refractory.

1.1.2 Description of identified studies

In total 14 cost-utility studies were identified in the systematic review and updates. Seven of these were described in detail in full papers or health technology assessment (HTA) submissions and were reviewed in detail and are summarised in Table 2.The model structure of the de novo model (described in section 1.2) was informed by a review of the previous modelling approaches.

Table 2. Summary list of other cost-effectiveness evaluations.

Study	Year	Country(ies) where study was performed	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
HTA 2007[1] (Green et al, 2009[2])	2007	England and Wales	Semi-Markov state transition model	NR	NR	BTZ versus HiDEX: £38,000
Hornberger et al, 2010[3]	2010	Sweden	Partitioned survival model	BTZ versus HiDEX: 0.04 BTZ versus LEN/DEX: 0.69	BTZ versus HiDEX: SEK 902,874 BTZ versus LEN/DEX: cost-saving	BTZ versus HiDEX: SEK 662,621 BTZ versus LEN/DEX: dominant
Moller et al, 2011[4]	2011	Norway	Discrete event simulation model	LEN/DEX versus BTZ: 0.76	LEN/DEX versus BTZ: NOK188,245	LEN/DEX versus BTZ: NOK247,048
NICE HTA 2009[5]	2009	England and Wales	Partitioned survival model	LEN/DEX versus BTZ (if 1 prior therapy): NR LEN/DEX versus DEX (if ≥ 2 prior therapies): 1.86 LEN/DEX versus DEX (if 1 prior therapy, THAL): 1.7	LEN/DEX versus BTZ (if 1 prior therapy): NR LEN/DEX versus DEX (if ≥ 2 prior therapies): NR LEN/DEX versus DEX (if 1 prior therapy, THAL): NR	LEN/DEX versus BTZ (if 1 prior therapy): £46,865 LEN/DEX versus DEX (if ≥ 2 prior therapies): £30,350[b] LEN/DEX versus DEX (if 1 prior therapy, THAL): £28,941[b]

Brown et al, 2013[6]	2013	England and Wales	Individual simulation model	LEN/DEX versus DEX in patients who have received 1 prior therapy: 2.2	LEN/DEX versus DEX in patients who have received 1 prior therapy: £66,483	LEN/DEX versus DEX in patients who have received 1 prior therapy: £30,153
Fragoulakis et al, 2013.[7]	2013	Greece	Discrete event simulation model	LEN/DEX versus BTZ: 0.79	LEN/DEX versus BTZ: €30,402	LEN/DEX versus BTZ: €38,268
NICE HTA 2014[8]	2014	England and Wales	Partitioned survival model	POM/LoDEX versus BTZ/DEX: 0.61 POM/LoDEX versus CTD: 0.61 POM/LoDEX versus BTD: 0.61	POM/LoDEX versus BTZ/DEX:£30,782 POM/LoDEX versus CTD: £47,219 POM/LoDEX versus BTD: £44,142	POM/LoDEX versus BTZ/DEX: £50,366 POM/LoDEX versus CTD: £77,915 POM/LoDEX versus BTD: £72,250

BTD, bendamustine plus thalidomide and dexamethasone; BTZ, bortezomib; CTD, cyclophosphamide plus thalidomide and dexamethasone; DEX, dexamethasone; HiDEX, high dose dexamethasone; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LoDEX, low dose dexamethasone; NICE, National Institute for Health and Care Excellence; NR, not reported; POM, pomalidomide; QALY(s), quality-adjusted life year(s); THAL, thalidomide. .

1.2 Restricted patient pool analysis

1.2.1 Patient population

The economic analysis presented in this Appendix considers patients with relapsed or relapsed and refractory MM who had at least two prior lines of treatment including an IMiD and a bortezomib based regimen (ie the approved FDA label and a likely alternative for the EMA label), and are suitable candidates for treatment with PANO/BTZ/DEX.

In an ideal situation such subgroup data would be available for the acknowledged comparator regimen of LEN/DEX. However, the two alternative datasets available from the pooled MM-009 and MM-010 LEN/DEX trials are the full population dataset (n = 353) and the subset of population data representing 2 to 3 prior lines (n = 220) presented by Stadtmauer et al, 2009[9]. It must also be noted that these patients had substantially different prior treatments as compared to any of the PANORAMA-1 patients reflecting the advances in MM treatment pathway during the previous decade. Hence finding a perfect match is not easy.

Since we have access to patient level data from the PANORAMA-1 trial, our strategy has been to identify the best available match to the above two available datasets on LEN/DEX, to serve as the basis for generating proxies (ie PFS and OS HRs) for the efficacy comparison that is required for the ultimate target population (ie prior IMiD, prior bortezomib and at least two prior lines of treatment).

Patient characteristics for PANO/BTZ/DEX were derived from the PANORAMA-1 trial[10]. The trial included a total number of 768 patients of which 387 patients (ie full analysis set [FAS]) were randomised to receive PANO/BTZ/DEX. Of these, 188 (nearly 49% of the study population active arm) had received 2 to 3 prior lines of treatment. Further restricting by the type of prior treatment, 73 patients (nearly 19% of the study population active arm) were identified who had received prior IMiD and prior bortezomib. The selected baseline patient characteristics are summarised in Table 3 below.

Table 3. Patient characteristics within PANORAMA-1 trial

Parameter	PANO/BTZ/DEX	
N	**387**	**73**
Population	ITT	Prior IMiD and BTZ and ≥ 2 prior LoT
Baseline age, median (range)	63 (28 to 84)	60 (33 to 79)
Male, N (%)*	52.2%	33 (45.2%)
ECOG performance status, n (%)		
0	45.2%	41 (56.1%)
1	49.4%	30 (41.1%)
2+	4.9%	2 (2.7%)
MM characteristic, n (%)		
Relapsed & refractory	63.8%	34 (46.6%)
Relapsed	34.6%	39 (53.4%)
Time since diagnosis (months), median (range)	37.1 (2.4 to 1275)	53.1 (11.6 to 164.8)

BTZ, bortezomib; DEX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory drug; ITT, Intention-to-treat; LoT, lines of treatment; MM, multiple myeloma; PANO, panobinostat.

1.2.2 Review of relevant modelling approaches

Several published pharmacoeconomic models in the indication of rrMM exist within the literature. Broadly speaking, the published models are consistent in terms of a number of integral features, ie they include pre-progression and post-progression health states in the model structure, they include adverse events, and they capture subsequent treatments. However, the models vary in terms of the chosen time horizon and the modelling approach, eg whether a partitioned survival model or microsimulation model is used.

A targeted literature review, searching in PubMed and on the National Institute for Health and Care Excellence (NICE) website, was conducted in order to identify and evaluate previously published pharmacoeconomic models and HTA submissions in the rrMM setting. The objective of the targeted search was twofold: firstly, to extract relevant model features, model drivers, and conduct a quality assessment of pharmacoeconomic models published in the last 5 years. Secondly, based on findings from the extraction and quality assessment, to decide as to which models (if any) could be suitable, perhaps with modifications for the current analysis. Table 4 shows a summary of features for the pharmacoeconomic models identified.

Table 4. Summary of published pharmacoeconomic models in the last years

Author	Treatments compared	Model type	Health states	Time horizon (Years)	Adverse events included	Country
Hornberger et al, 2010[3]	BTZ DEX LEN/DEX	Partitioned survival model	Pre-progression Post-progression Death	10	Yes	Sweden
Brown et al, 2013[6]	DEX LEN/DEX	Individual simulation model	Pre-progression Post-progression Death	30	Yes	England and Wales
Fragoulakis et al 2013[7]	LEN/DEX BTZ	Discrete event simulation model	Pre-progression Post-progression Death	Individual level lifetime	Yes	Greece
Möller et al, 2011[4]	LEN/DEX BTZ	Discrete event simulation model	Pre-progression Post-progression Death	Individual level lifetime	Yes	Norway
Green et al, 2009[2]	BTZ HiDEX	Semi-Markov state-transition model	On treatment regimen *i* Death whilst on treatment regimen *i*	15 years	No	England, Wales
NICE HTA 2007[1]	BTZ HiDEX	Semi-Markov state-transition model	NA	NA	Yes	England, Wales
NICE HTA 2009, 2013[5]	LEN/DEX BTZ BEN and other chemotherapy agents	Partitioned survival model	Pre-progression on Tx Pre-progression off treatment Post-progression	25 years	Yes	England, Wales
NICE HTA 2014[8]	POM BTZ/DEX THAL/DEX/CYC BEN/THAL/DEX	Partitioned survival model	Pre-progression on Tx Pre-progression off treatment Post-progression	25 years	Yes	England, Wales

BEN, bendamustine; BTZ, bortezomib, CYC, cyclophosphamide; DEX, dexamethasone; HiDEX, high dose dexamethasone; HTA, Health technology Assessment; LEN, lenalidomide; NA, not applicable; NICE, National Institute for Health and Care Excellence; POM, pomalidomide; THAL, thalidomide; Tx, treatment.

Altogether eight economic evaluations were reviewed. The economic evaluations were fairly recent; the earliest was published in 2007 whereas the latest was published in 2014. Three submission dossiers were identified for England and Wales, other studies were published for Sweden, Norway, and Greece. Except for one case, all studies conducted a cost-utility analysis, where the main model outcome was the ratio of the incremental costs of the new treatment and its incremental quality-adjusted life years (QALY) compared with standard

treatment(s). The time horizon of the models varied between 10 and 30 years. Semi-Markov, partitioned survival and discrete event simulation[1] modelling approaches were used.

The structure of the current model was informed by the review of previous modelling approaches, the treatment paradigm and the treatment pathways of rrMM.[11] After careful consideration, developing a partitioned survival model[122] along the pivotal PANORAMA-1 trial was deemed most appropriate for the following reasons:

- Consistent with previous models, the panobinostat model consists of three key health states: pre-progression, post-progression, and death. Furthermore, the pre-progression health state is stratified according to whether a patient receives treatment or not in order to capture the utility and resource use implications. Off-treatment health state, referring to the situation when patients are progression-free but receive no treatment, has been considered in two recent NICE HTA submission models as well.[5,8] Reflecting the treatment pathways in rrMM, the post-progression health state is further stratified to allow for patients to receive subsequent antineoplastic treatments and/or further supportive care.[13]
- Microsimulation models accurately describe the treatment pathways of a disease however they are not user friendly because of the complexity and the typically long computation time they entail. As such, they do not always serve the purpose of pricing and reimbursement activities. While both microsimulation and partitioned survival models have been published in the literature, a partitioned survival modelling approach was preferred because of the transparency, reproducibility, and tractability it offers.
- The model structure allows the clinical benefits of PANO/BTZ/DEX to be captured, in particular the 5.02 months (mean) treatment free interval (TFI) associated with a 6.42 months (mean) treatment duration and a 11.43 months (mean) PFS within the targeted patients segment (see section 4).
- Results of indirect treatment comparisons (eg HRs of progression and death) can be incorporated easily into the model.

[1] In fact, a single microsimulation model was adapted to several countries

[2] In a partitioned survival model the number of patients in each health state at any time is determined directly from the underlying survival curves of a trial. Sometimes, it is preferred to a conventional Markov approach because it may avoid making challenging assumptions, such as whether death is permitted from all health states. A partitioned survival approach does not necessarily incorporate tracking of patients or explicit transitions (although in practice, the use of transition probabilities in the models are often done).

1.2.3 Model structure

A decision analytic partitioned survival model was developed having the structure shown in Figure 1 highlighting the considered health states and possible transitions between those[3.] The model captures three key aspects of MM that are affected by disease progression and the effects of treatment, namely survival, HRQL and costs. The health states in the model are identical to those used in previous recent models submitted for NICE technology appraisals.[8,14,15] Disease progression is implemented through patients moving from the two pre-progression health states to the post-progression health state, corresponding to fourth-line therapy, that is a) POM/DEX together with further supportive care (Medical Resource Utilisation, MRU)[4],[13] or b) other active treatments together with further supportive care, or c) supportive care alone, and finally to the to the death health state. The modelled fourth-line treatment options are referred to as last line of treatment (LLoT).

The model consists of three key health states: pre-progression, post-progression, and death. Two pre-progression health states are differentiated, one corresponding to when a patient is receiving treatment (pre-progression, Tx1) and a second corresponding to when a patient is progression-free but receives no treatment (pre-progression, no Tx1). These two health states have been considered in two recent NICE HTA submission models,[5,15] and enable the model to capture the utility and resource use implications of being on or off treatment. The post-progression state included is to capture the LLoT as described above.

The model structure corresponds to the clinical practice[5] in that it adopts the view that patients who discontinue treatment for reasons other than progression or relapse can remain without antineoplastic treatment until they experience progression, ie, treatment is rarely initiated immediately after discontinuation[6].

An assumption was made that after PANO/BTZ/DEX treatment patients would move to LLoT directly, as they do when progressing or discontinuing the third line LEN/DEX treatment. Once, LEN/DEX treatment is accounted for as part of the LLoT as reported by Gooding et.al.[13] Secondly, since we are applying a single survival curve on PANO/BTZ/DEX to inform risk of death while in post progression health state, by adding an extra treatment, only the

[3] Section 4 presents the PFS profile of the prior IMiD and prior bortezomib and ≥ 2 prior lines population of the PANORAMA-1 trial divided into on- and off-treatment periods.

[4] Medical-resource utilisation incorporates clinical attendance, inpatient admissions, transfusions, supportive therapy, blood tests as described by ASH 1727, Gooding et.al.

[5] Based on clinicians feedback collected by Novartis.

[6] In the PANORAMA-1 trial, only 23 (6%) out of the 387 patients were censored for receiving a new cancer therapy (First Interpretable Results – December 2013).

overall cost would increase, while no LY/QALY benefit would be added. We could have added LEN/DEX *instead of* POM/DEX into the LLoT basket, however there is no evidence to support the replacement of POM/DEX with LEN/DEX in the UK treatment pathway.

Patient flow within the model

Pre progression, Tx1 health state

Patients receive either PANO/BTZ/DEX or LEN/DEX treatment. Once receiving therapy, they are subject to early discontinuation of treatment due to progression or relapse[7], to early discontinuation of treatment due to reasons other than progression, and death.

- *Discontinue due to progression:* patient starts receiving further treatment (ie. transition from 'pre-progression, Tx1' health state to 'post-progression' health state).
- *Discontinue due to reasons other than progression:* patient starts a treatment free interval (TFI) (ie transition from 'pre-progression, Tx1' health state to the 'pre-progression, no Tx1' health state).
- *Discontinue due to treatment completion:* as an option is limited to PANO/BTZ/DEX in line with PANORAMA-1 protocol and anticipated label that is limiting the treatment duration to 48 weeks (ie transition to the 'pre-progression, no Tx1' health state).[8]

Pre-progression, no Tx1 health state

Patients beyond being monitored, do not receive any antineoplastic agent. They are subject progression and death. Upon progression patient starts receiving further treatment (ie transition from 'pre-progression, no Tx1' health state to 'post-progression' health state).

Post-progression health state

Once patients enter the 'post-progression' health state, they are assumed to receive post-progression treatment until death and no further progression (and hence explicit treatment switch) in the model is allowed. The post-progression treatment was handled as a mix of various therapies.

Death health state

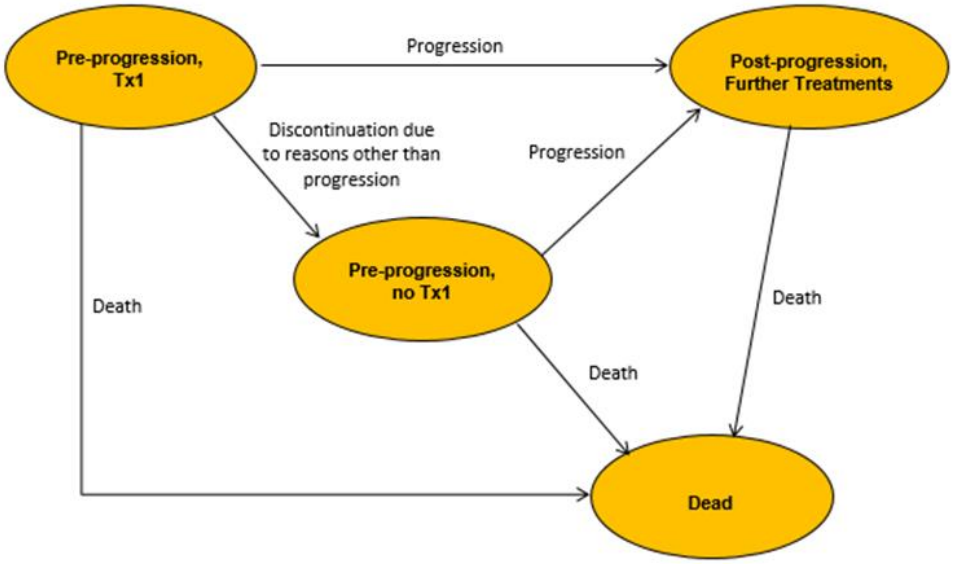
Patients are at risk of dying at all points of the model and can move to the 'Death' health state from any other health state.

Key features of the model are summarised in Table 5.

[7] Only 'progression' is used hereafter but referring to both progression and relapse

[8] Patient on the LEN/DEX arm were treated until progression in line with its label, unless discontinued due to reasons other than progression or treatment completion.

Figure 1. Structure of the decision analytic partitioned survival model



Note: Treatment 1 (Tx1) in the health economic model structure does not refer to the first treatment of newly diagnosed MM patients or does not represent the absence of any prior treatment for MM.

Table 5. Key features of analysis.

Factor	Chosen value	Justification	Flexibility	Reference
Time horizon	25 years	Appropriate timescale for evaluating conditions with high death rates such as rrMM, to enable capturing (differential) costs and outcomes	Flexibility includes time horizons ranging from "trial period" to 25 years	Guide to the methods of technology appraisals[16]
Cycle length	3 weeks	Reflects the drug administration schedule in the PANORAMA-1 trial	Fixed[9]	San Miguel et al, 2014[10]
Half-cycle correction	Applied	Consistent with previous economic models and the NICE Guide to the methods of technology appraisals	Fixed	NICE technology appraisals for BTZ,[15] LEN[5] and POM[8]; Guide to the methods of technology appraisals[16]
Were health effects measured in QALYs; if not, what was used?	Life years (LYs) and quality-adjusted life years (QALYs)	Consistent with previous economic models and the NICE Guide to the methods of technology appraisals	Outcomes such as "Life years gained" and "Time spent off-treatment" are presented	NICE technology appraisals for BTZ, LEN and POM Guide to the methods of technology appraisals[16]
Discounting	Effects: 3.5% Costs: 3.5%	Consistent with the NICE Guide to the methods of technology appraisals	Flexible: any values can be implemented	Guide to the methods of technology appraisals[16]
Analysis perspective	Healthcare system (NHS/PSS)	Consistent with the NICE Guide to the methods of technology appraisals	Direct costs are included, Option to include indirect costs	Guide to the methods of technology appraisals[16]

BTZ, bortezomib; LEN, lenalidomide; LY(s), life year(s); NHS, National Health Service; NICE, National Institute for Health and Care Excellence; POM, pomalidomide; PSS, personal social services; QALYs, quality-adjusted life years; rrMM, relapsed/refractory multiple myeloma.

1.2.4 Intervention technology and comparators

In the model, the intervention, PANO/BTZ/DEX is implemented for a restricted pool of patients as part of the anticipated marketing authorisation and is given according to the recommended

[9] The different cycle length for lenalidomide and pomalidomide has been accounted for in all cost calculations

regimen and that utilized in the PANORAMA-1 trial (see section 4.3 in the main submission dossier). The comparator, LEN/DEX, is also implemented with restriction, but in line with NICE TA171 Guidance and according to the recommended regimen. The comparator, LEN/DEX, is also implemented as per the marketing authorisation and according to the recommended regimen.

1.3 Clinical parameters and variables

1.3.1 Methodology

As described above (section 1.2), in the health economic model patients' survival is partitioned into pre-progression and post-progression periods, of which the pre-progression period is further divided into on-treatment and off-treatment intervals.

To model the flow of patients through the different health states over time, transition probabilities were estimated by *post-hoc* analyses of patient-level data from the PANORAMA-1 trial, ie. the probabilities of PFS (progression or pre-progression death), discontinuation or post progression death were estimated by fitting parametric models[10] onto Kaplan–Meier curves generated from patient level data specific to that of the targeted subpopulation (after prior IMiD, bortezomib and ≥ 2 prior lines of treatment).

Given that there is no known data for such a subpopulation on LEN/DEX,[9,17] (ie LEN/DEX has never been tested in a clinical trial environment in the patients in which it is currently used) the equivalent transition probabilities were generated as values relative to those of PANO/BTZ/DEX.

These relative values (ie HRs) were established by matching the two treatments within their own, separate "environment". Two sub-populations were tested to generate HRs: the full trial populations of the two treatments; and the subpopulation of patients who had received 2 to 3 prior lines of treatment.

The model runs on these measured (PANO/BTZ/DEX) and relative (LEN/DEX) efficacy parameters, based on the assumption that the relative efficacy of LEN/DEX versus PANO/BTZ/DEX established within those two different subgroups also applies in the targeted

[10] Five parametric survival models (exponential, Weibull, log-logistic, log-normal, Gompertz) were fitted on Kaplan–Meier plots of the individual patient-level PFS data. The regression models were compared visually, assessed using Akaike information criterion (AIC) and Bayesian information criterion (BIC) as well as by clinical plausibility to determine their relative fit to the observed trial data.

subgroup of interest in this economic analysis (that is, after prior IMiD, bortezomib and ≥ 2 prior lines of treatment).

Table 6 summarises the ways transition probabilities were derived and their place of use in the model.

Table 6. Approaches used to derived transition probabilities and their use in the economic model

Parameter	Data source	Model used for base case	Use of transition probabilities
PANO/BTZ/DEX			
Risk of progression or death	PANORAMA-1, PANO/BTZ/DEX arm Patient-level PFS data	Weibull	Pre-progression, Tx1, PANO/BTZ/DEX
Risk of treatment discontinuation	PANORAMA-1, PANO/BTZ/DEX arm Patient-level treatment duration data	Exponential	Pre-progression, Tx1, PANO/BTZ/DEX
Risk of death	PANORAMA-1, PANO/BTZ/DEX arm Patient-level OS data	Gompertz	Post-progression (derived as OS-PFS) PANO/BTZ/DEX
Risk of experiencing adverse events	PANORAMA-1, PANO/BTZ/DEX arm Patient-level AE data	Occurrence probability	Pre-progression, Tx1, PANO/BTZ/DEX
LEN/DEX[a]			
Risk of progression or pre-progression death (relative to PANO/BTZ/DEX)	Simulated patient level data from MM-009/010, published Kaplan–Meier plot for PFS	Hazard ratio	Pre-progression, Tx1, LEN/DEX
Risk of treatment discontinuation	Median PFS and median treatment duration published for MM-009/010	Hazard ratio	Pre-progression, Tx1 PANO/BTZ/DEX
Risk of death (relative to PANO/BTZ/DEX)	Simulated patient level data from MM-009/010, published Kaplan–Meier plot for PFS	Hazard ratio	Post-progression, Tx1 (derived as OS-PFS) LEN/DEX

[a] For LEN/DEX, to keep the model parsimonious, exponential distribution was applied.

AE, adverse event; BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; Tx, treatment.

San Miguel et al. 2013;[18] Dimopoulos et al 2009[17] Stadtmauer et al 2009[9]

1.3.2 Clinical input parameters for PANO/BTZ/DEX

Type of data retrieved

To derive the transition probabilities for PANO/BTZ/DEX, the following types of patient level data were used via *post hoc* analysis from the PANORAMA-1 trial:

- Progression-free survival (PFS, the primary endpoint of the PANORAMA-1 trial)[11]
- Exposure to treatment
- Overall survival (OS).

Type of probabilities generated

Parametric survival models were fitted on the Kaplan–Meier curve generated on subgroup specific (ie patients with at least two prior lines of treatment including an IMiD and bortezomib) patient-level data to estimate the following transition probabilities for PANO/BTZ/DEX:

- Risk of progression or pre-progression death (based on PFS data)
- Risk of treatment discontinuation (based on exposure to treatment data)
- Risk of death (based on OS data).

The sections below provide a detailed description of the three types of patient-level time to event data, as well as introducing the parametric survival models fitted to derive the three types of transition probabilities also listed above.

Risk of progression or pre-progression death (PFS)

The risk of experiencing a PFS event (ie either progression or death) in a given cycle was estimated using patient-level data from the PANORAMA-1 trial. Time since randomisation until progression or death (ie an event) or censoring was considered as exposure time. Table 7 provides descriptive statistics for the derived time to PFS event dataset.

Table 7. Descriptive statistics on the derived time to PFS event, prior IMiD and bortezomib and ≥ 2 prior lines of treatment

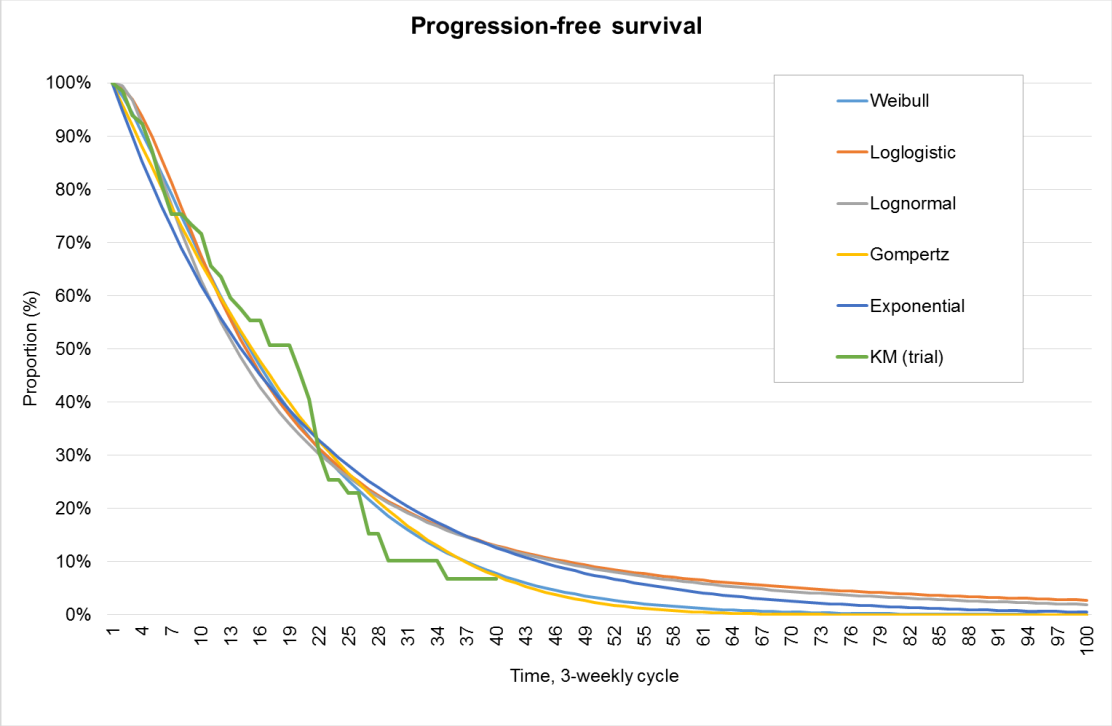
Time to PFS event	Characteristic	Patients
PANO/BTZ/DEX, N = 73	No. of events – n (%)	44 (60.3%)
	No. of censored – n (%)	29 (39.7%)

Event corresponds to a patient who progressed or died; censored corresponds to a patient who was censored for PFS before progression, death or given further anti-cancer therapy.
BTZ, bortezomib; DEX, dexamethasone; IMiD, immunomodulatory drug; PANO, panobinostat; PFS, progression-free survival.

[11] PFS was determined based on modified EBMT criteria as per investigator's assessment.

Five distributions (exponential, Weibull, log-logistic, log-normal, Gompertz) were fitted on the individual patient-level PFS data to smooth and extrapolate PFS curves beyond the trial period and to derive the transition probabilities.

Figure 2. PFS Kaplan–Meier curve and fitted parametric models for the population with prior IMiD and bortezomib and ≥ 2 prior lines of treatment



Based on the AIC and BIC statistics as well as visual assessment, for the subpopulation with prior IMiD and immunomodulatory drug and ≥ 2 prior lines of treatment the **Weibull** distribution was judged to provide the best model for all three curves (Figure 3). However, the AIC and BIC are relatively similar between the Gompertz and Weibull distributions therefore it may be difficult to discriminate between them[12]. Table 8 summarises the AIC and BIC values calculated for the various survival models.

[12] Please see Table 41 for scenario analysis

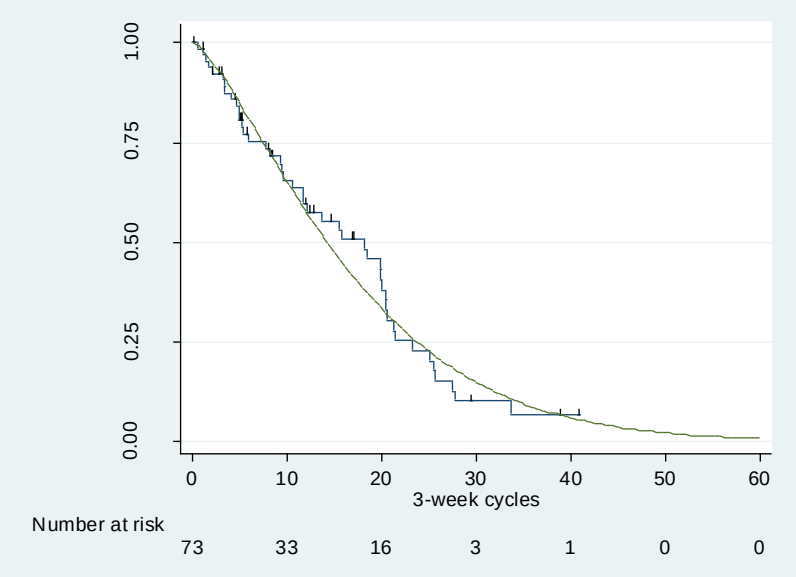
Table 8. AIC and BIC statistics for the PFS models: subpopulation with prior IMiD and bortezomib and ≥ 2 prior lines of treatment

Model	AIC	BIC
Exponential	153.2326	155.5231
Weibull	***149.5801***	***154.1611***
Lognormal	156.7057	161.2866
Loglogistic	155.0865	159.6674
Gompertz	149.6936	154.2745

The best fitting model selected for the base case analysis is shown in bold

AIC, Akaike information criterion; BIC, Bayesian information criterion; IMiD, immunomodulatory drug; PFS, progression-free survival.

Figure 3. Kaplan–Meier curve and fitted Weibull model for PFS: subpopulation with prior IMiD and bortezomib and ≥ 2 prior lines of treatment



IMiD, immunomodulatory drug; PFS, progression-free survival.

Risk of treatment discontinuation

The risk of treatment discontinuation in a given 3-weekly cycle – to determine the proportion of patients who are on- and off-treatment in each cycle – was estimated using patient-level treatment discontinuation data from PANORAMA-1 trial (safety set[13] (n = 72) of the targeted subpopulation with at least two prior lines of treatment including an IMiD and bortezomib)

[13] Patients who received at least one dose of study treatment (n = 72/73) in the subpopulation with at least two prior treatments including an IMiD and bortezomib

In particular, treatment discontinuation data was used applying survival analyses methods. The length of treatment exposure for a patient was considered the time to treatment discontinuation. All patients discontinued treatment before or at the time of a PFS event; thus no patient was censored.

The median treatment duration was 4.2 months (6.1 model cycles) for the subpopulation with at least two prior lines of treatment including an IMiD and bortezomib.

Contrary to the PANORAMA-1 trial protocol and the anticipated licence, some patients in the PANORAMA-1 trial had a documented treatment duration of greater than 48 weeks. In order to accurately capture the efficacy related cost of the treatment as per the clinical trial, these patients were not censored in the model. However, the proportions of patients continuing beyond cycle 20 are very low (proportion of patients receiving PANO/BTZ/DEX in cycle 20: 1.3%[14]).

Five distributions (Exponential, Weibull, log-logistic, log-normal, Gompertz) were fitted on the individual patient-level data to smooth the time to treatment discontinuation curves and to derive the transition probabilities. Curves were smoothed until 48 weeks, at which point the proportion of patients on treatment dropped sharply (in line with the trial protocol as described above). Beyond 48 weeks treatment discontinuation rates were not smoothed.

Based on the AIC and BIC statistics as well as visual assessment, for the subpopulation with prior IMiD and bortezomib and ≥ 2 prior lines of treatment the **exponential** distribution was judged to provide the best model for PANO/BTZ/DEX and was selected for the base case setting of the health economic model. No extrapolation of the curves (and hence the transition probabilities) was needed since all patients discontinued the treatment.

Figure 4 presents the Kaplan–Meier and best fitting curves and Table 9 summarises the AIC and BIC values calculated for the various survival models.

[14] Proportion of patients with prior IMiD and bortezomib and ≥ 2 prior lines continuing with PANO/BTZ/DEX beyond cycle 16: cycle 17, 15.5%; cycle 18, 5.8%; cycle 19, 2.1%; cycle 20, 1.3%.

Table 9. AIC and BIC statistics for the treatment discontinuation models: subpopulation with prior IMiD and bortezomib and ≥ 2 prior lines of treatment

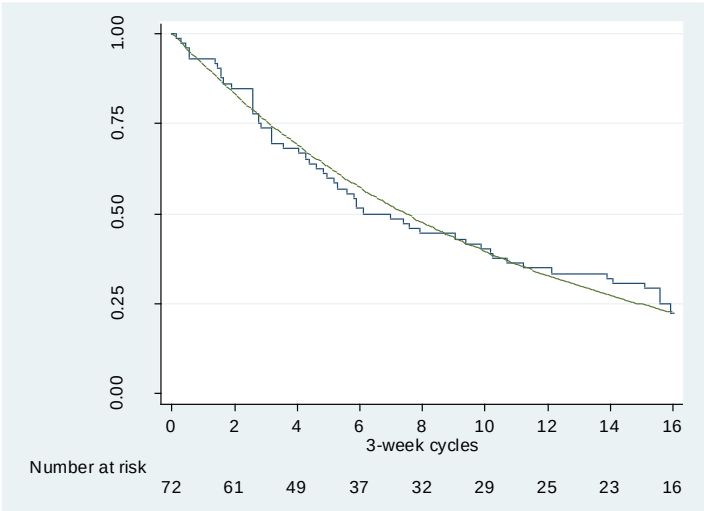
	PANO/BTZ/DEX	
Model	**AIC**	**BIC**
Exponential	***224.0727***	***226.3494***
Weibull	226.0652	230.6185
Lognormal	226.4784	231.0317
Loglogistic	225.1913	229.7447
Gompertz	225.7766	230.3299

The best fitting model selected for the base case analysis is shown in bold

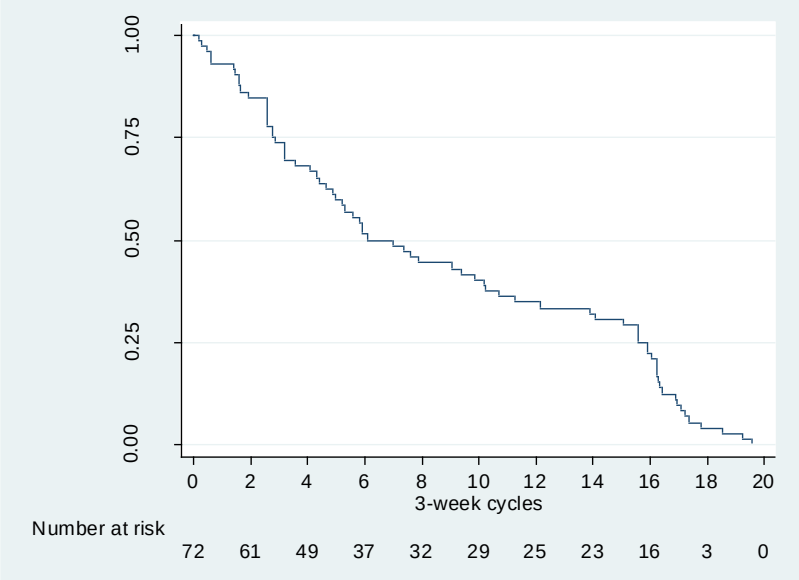
AIC, Akaike information criterion; BIC, Bayesian information criterion; BTZ, bortezomib; DEX, dexamethasone; IMiD, immunomodulatory drug; PANO, panobinostat.

Figure 4. Proportion of patients without treatment discontinuation: subpopulation with prior IMiD and bortezomib and ≥ 2 prior lines of treatment; a) Kaplan–Meier curve and fitted parametric models (PANO/BTZ/DEX – exponential model) for 48 weeks b) Kaplan–Meier curve presenting full follow-up data

a) PANO/BTZ/DEX – exponential model (48 weeks)



b) PANO/BTZ/DEX – full follow up data



BTZ, bortezomib; DEX, dexamethasone; IMiD, immunomodulatory drug; PANO, panobinostat.

Risk of death

The risk of experiencing a PFS event (ie either progression or pre-progression death) in a given cycle was estimated using patient level data of the PANORAMA-1 trial (as described above).

Similarly, to estimate the risk of death, individual patient-level survival data of the PANORAMA-1 trial was utilized. For the OS analysis, time since randomisation until death (ie event) or censoring was treated as exposure time. Patients were censored at the last contact date if they were lost to follow-up for survival status measurement.

Table 10 provides descriptive statistics about the derived OS datasets for the two subpopulations.

Table 10. Descriptive statistics on the derived overall survival dataset: subpopulation with prior IMiD and bortezomib and ≥ 2 prior lines of treatment

Time to death	Characteristic	Patients
PANO/BTZ/DEX, N = 73	No. of events – n (%)	[redacted]%)
	No. of censored – n (%)	[redacted]%)

BTZ, bortezomib; DEX, dexamethasone; IMiD, immunomodulatory drug; PANO, panobinostat.

Five distributions (exponential, Weibull, log-logistic, log-normal, Gompertz) were fitted on the individual patient-level data to smooth and extrapolate the OS curves.

Figure 5. Overall survival Kaplan–Meier curve and fitted parametric models for the population with prior IMiD and bortezomib and ≥ 2 prior lines of treatment

Based on the AIC and BIC statistics, visual assessment as well as assessing clinical plausibility, for the subpopulation with at least two prior lines of treatment including an IMiD and bortezomib, the **Gompertz** distribution was judged to provide the best model for PANO/BTZ/DEX and was selected for the base case setting of the health economic model. The Weibull and Gompertz models imply increasing mortality risk, the exponential model implies constant mortality risk in the long run. From a clinical perspective, the prediction of decreasing mortality rates over the lifetime (implied by a log-logistic or lognormal model) is unlikely to be plausible; modelling increasing or constant mortality may be more appropriate. Therefore, the Weibull, the Gompertz and the exponential models were preferred prior to model fitting and the best fitting model used for the base case analysis was selected from these three.

Figure 6 presents the Kaplan–Meier and modelled OS curves and Table 11 summarises the AIC and BIC values calculated for the various regression models.

Table 11. AIC and BIC statistics for the Weibull regression models for risk of death: subpopulation with prior IMiD and bortezomib and ≥ 2 prior lines of treatment

	PANO/BTZ/DEX	
Model	**AIC**	**BIC**
Exponential	*156.6188*	*158.9092*
Weibull	157.118	161.6989
Lognormal	156.2662	160.8471
Loglogistic	157.7086	162.2895
Gompertz	**157.3257**	**161.9066**

The best fitting model (exponential) was not selected for the base case analysis based on assessment of clinical plausibility

AIC, Akaike information criterion; BIC, Bayesian information criterion; BTZ, bortezomib; DEX, dexamethasone; IMiD, immunomodulatory drug; PANO, panobinostat.

Figure 6. Kaplan–Meier curve and fitted Weibull overall survival model: subpopulation with prior IMiD and BTZ bortezomib ≥ 2 prior lines of treatment

BTZ, bortezomib; IMiD, immunomodulatory drug.

1.3.3 Clinical input parameters for LEN/DEX

The efficacy of LEN/DEX (ie PFS, and OS) was estimated by indirect treatment comparisons between PANO/BTZ/DEX and LEN/DEX.

The purpose of this indirect treatment comparison is to measure the relative efficacy LEN/DEX against PANO/BTZ/DEX in the targeted population (ie with at least two prior treatments including an IMiD and bortezomib) such that it can be used for health economic modelling purposes.

Because no published efficacy data are available for LEN/DEX in patients who had received prior IMiD, bortezomib, and two prior lines of treatment, it was not feasible to compare the efficacy of PANO/BTZ/DEX with the efficacy of LEN/DEX in this particular patient population. Hence the transition probabilities required to model the flow of LEN/DEX patients through the different health states over time were generated as values relative to those of PANO/BTZ/DEX.

These HRs of PFS and OS allowed linking the efficacy of PANO/BTZ/DEX to the efficacy of LEN/DEX to obtain clinical input parameters for LEN/DEX for the health economic model.

Such relative values (ie HRs) could be established by matching the two treatments within their own, separate “environment” yet as similar as possible.

Efficacy data for LEN/DEX have been published for the full LEN/DEX trial populations[17] and for patients who received 2 to 3 prior treatments.[9] After deriving similar data from the PANORAMA-1 full data set by comparing the PFS and OS figures of those of PANO/BTZ/DEX and LEN/DEX, HRs of PFS and OS were estimated individually on these two sets of populations.

Generating HRs for PFS and OS

In terms of PFS and OS, four indirect treatment comparison methods were explored. The indirect treatment comparisons yielded estimates of HR of PFS and OS between LEN/DEX and PANO/BTZ.DEX. HRs were estimated for the full trial populations as well as for the similar subpopulations with 2 to 3 prior lines of treatment. Subsequently it was assumed that these HRs were applicable to the subgroup under study, ie the subpopulation with at least two lines of prior treatment including an IMiD and bortezomib. In other words, this assumption implied that, for example, the relative risk of death estimated for LEN/DEX against PANO/BTZ/DEX based on the intent to treat populations would be the same in patients who had received prior IMiD, bortezomib and two prior lines of treatment.

While such an assumption is limiting, it was necessary due to the lack of relevant data.

Table 12 provides a brief summary of the methods applied and the generated PFS and OS HRs for the full population and for the subpopulation with 2 to 3 lines of prior treatment. For

detailed description of the four methodologies, please see section 4.10.4 on 'methods of analysis and presentation of results' in the main submission dossier.

Table 12. Summary of the methods used for indirect treatment comparison and the advantage and disadvantages of the methodologies as used in this analysis

	Common comparators method	**Naive comparison**	**Unadjusted Cox regression**	**Matching adjusted indirect treatment comparison (Cox regression)**
Comparators considered	BTZ/DEX, BTZ, DEX, LEN/DEX, BTZ/DOX	LEN/DEX	LEN/DEX	LEN/DEX
Study population employed in the comparison	ITT population	ITT population; 2 to 3 prior LoT	ITT population; 2-3 prior LoT	ITT population; 2-3 prior LoT
Adjustment to patient population differences	Implicitly assumes that relative efficacy measures are comparable	No adjustment for patient characteristics	No adjustment for patient characteristics	PANORAMA-1 population was adjusted to the MM-009/010 populations in terms of patient selection and baseline patient/ disease characteristics
Data type used	Aggregate data	Aggregate data	• Patient level data (PANO/BTZ/DEX) • Simulated patient level data for OS and PFS (LEN/DEX)	• Patient-level data (PANO/BTZ/DEX) • Simulated patient level data for OS and PFS (LEN/DEX) • Aggregate data for baseline characteristics (LEN/DEX)
Advantages of the methodology	Established methodology	Simple and transparent	• Use of patient level data • Patient numbers are not affected by matching	• Can adjust for baseline characteristics including relative treatment effect modifiers • By matching patient populations this approach mimics randomization
Disadvantage	• Assumes factors that may influence the relative treatment	• No randomization • No adjustment	• Assumes proportional hazard assumption which may not be true	• Does not adjust for unobserved differences between trials • Matching

	effect (eg, HR) are balanced across the trials in the evidence network • May be large uncertainty around the outcomes as observed in this case for LEN/DEX versus PANO/BTZ/DEX)	to differences in patients or in trial design between studies		performed only for shared variables • Assumes proportional hazard assumption which may not be true
Outcomes compared (relative efficacy measure)	• PFS (HR) • TTP (HR) • CR/nCR (OR) • OS (HR)	• PFS (HR) • OS (HR)	• PFS (HR) • OS (HR)	• PFS (HR) • OS (HR)
Context applied in health economic model	• Third line treatment	• Third line treatment	• Third line treatment	• Third line treatment

BTZ, bortezomib; CR, complete response; DEX, dexamethasone; DOX, doxorubicin; HR, hazard ratio; ITT, Intention-to-treat; LEN, lenalidomide; LoT, lines of treatment; nCR, near-complete response; OR, odds ratio; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; TTP, time to progression.

Table 13. PFS and OS HRs comparing the efficacy of LEN/DEX versus PANO/BTZ/DEX

		PFS		OS	
		HR	SE	**HR**	SE
Full trial population based	Common comparator method[15]	**1.870**	0.356	**1.216**	0.384
	Naïve comparison[16]	**1.081**	0.216	**1.006**	0.201
	Unadjusted Cox[17]	**0.929**	0.104	**0.997**	0.131
	MAIC[18]	**1.002**	0.126	**1.052**	0.157

[15] For further information (population specific PFS and OS data) please see table 24 in the main submission dossier

[16] For further information (population specific PFS and OS data) please see table 25/a in the main submission dossier

[17] For further information (population specific PFS and OS data) please see table 26/a in the main submission dossier

Based on the subpopulation with 2 to 3 lines of prior treatment	Naïve comparison[19]	**1.190**	0.238	**0.959**	0.192
	Unadjusted Cox[20]	**1.061**	0.145	**1.075**	0.179
	MAIC[21]	**1.108**	0.331	**1.413**	0.424

HR, hazard ratio; MAIC, matching adjusted indirect treatment comparison; PFS, progression-free survival; SE, standard error

Treatment discontinuation

While PFS and OS between LEN/DEX and PANO/BTZ/DEX can be compared with indirect treatment comparison, the comparison of treatment durations with such methods is not feasible because LEN/DEX is a continuous treatment. Instead, a simple method was used which utilized the median PFS and the median treatment duration published for either the full trial population (11.1 and 10.1 months, respectively) or the subpopulation with 2 to 3 prior lines of treatment (9.5 and 9.2 months, respectively). In particular, it was assumed that the risk of treatment discontinuation for the full population is 9.9% times higher (that is, 11.1 / 10.1) than the risk of PFS in each model cycle. In contrast for the subpopulation, the risk of discontinuation is assumed to be 3.3% higher than the risk of PFS in each model cycle. Thus, given the rate of progression or pre-progression death, the rate of treatment discontinuation was simply multiplied by this estimated HR.

Although the results will be presented using all seven scenarios (ie four for the full population and three for the restricted patient pool with 2 to 3 lines of prior treatment), the various sensitivity analysis will be performed only for the base case.

1.4 Measurement and valuation of health effects

Multiple myeloma is an incurable disease; patients diagnosed with rrMM often suffer with pronounced symptoms and thus a decreased health-related quality of life (HRQL)[19] See section 3 in the main submission dossier. Maintaining good HRQL is an important goal in the care of people with myeloma.[20] The uncontrolled growth of myeloma cells has many consequences, including skeletal destruction, bone marrow failure, suppression of normal

[18] For further information (population specific PFS and OS data) please see table 28/a in the main submission dossier

[19] For further information (population specific PFS and OS data) please see table 25/b in the main submission dossier

[20] For further information (population specific PFS and OS data) please see table 26/b in the main submission dossier

[21] For further information (population specific PFS and OS data) please see table 28/b in the main submission dossier

immunoglobulin production and renal insufficiency. Symptoms include: bone pain, fatigue, infectious complications and reduced physical function and mobility.[20,21] There is evidence that patients with myeloma report more symptoms and problems than those with other haematological cancers.[22]

In addition to the physical symptoms MM patients can suffer considerably from fear of recurrence and uncertainty about the future due to the relapsing nature of the disease and limited effectiveness of available treatments. This uncertainty combined with the burden of treatment and possible frustration with the limited treatment options can lead to patients feeling a loss of independence and inability to plan for the future.[20]

1.4.1 Health-related quality of life data from clinical trials

In the PANORAMA-1 trial, the EORTC QLQ-C30 questionnaire and the MM-specific module, EORTC-MY20, were used to provide patient-reported outcome measures of HRQL, disease symptoms and treatment-related adverse events. The EORTC QLQ-C30 and EORTC QLQ-MY20 are frequently employed in clinical trials of patients with MM and are recognised as reliable and valid measures.[23] The EORTC QLQ-C30 includes five functional dimensions (physical, role, emotional, cognitive, and social), three symptom items (fatigue, nausea/vomiting, and pain), six single items (dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea and financial impact) and a global health and quality-of-life scale (GHS). The EORTC QLQ-MY20 was used in conjunction with the EORTC QLQ-C30 and provides an additional 20 items grouped into four domains: symptoms, treatment adverse events, social support and future perspective. The recall period for both measures is the past week. For both questionnaires, scores are averaged and transformed linearly to a score ranging from 0 to 100 with high scores being indicative of better functioning for the QLQ-C30 functional domains and GHS/quality of life and better outcomes for QLQ-MY20 Future perspective and Body Image, while for the QLQ-C30 symptom scores and single items, together with the QLQ-MY20 Disease Symptoms and Side Effects of Treatment domains, low scores are indicative of fewer symptoms or side effects.

The EORTC QLQ-C30 and EORTC QLQ-MY20 were administered at screening and before study drug treatment on cycle 1 day 1 (C1D1) and every six weeks thereafter (ie C3D1, C5D1, C7D1, C9D1, C10D1, C11D1, C12D1), and during the study completion visit, but assessments were not performed in patients who discontinued treatment early (eg due to adverse event or disease progression) and were not continued during follow-up after completion of treatment (whether in remission or on disease progression). The measures were administered sequentially at the beginning of the study visit prior to any interaction with

the study physician (including any tests, treatment or receipt of results from any tests) to avoid biasing the patient.

However, the EORTC QLQ-C30 and EORTC QLQ-MY20 cannot be used directly in economic evaluation as they do not provide preference based utilities as are required for use in the economic model. A mapping approach was therefore employed.

1.4.2 Mapping

For the detailed description of the mapping, please see 5.4.2 in the main submission dossier.

Patients in the PANORAMA-1 trial with complete EORTC QLQ-C30 information on these four items were selected for inclusion in the mapping. For each included patient at each measured time point the QLQ-C30 value was mapped to obtain the corresponding EQ-5D utility value using the mapping algorithm described above. No adjustment was applied in case mapped values were higher (or lower) than the maximum (or minimum) EQ-5D utility score. Adjustment to baseline patient characteristics was not feasible. Cycle-specific as well as overall average and median utility values were estimated for the treatment arms.

Results

The overall mean (standard deviation [SD]) and median utility values were estimated to be 0.679 (SD = 0.182) and 0.696 for PANO/BTZ/DEX.

Because no preference based utility data was available for LEN/DEX treatment in this subpopulations, two scenarios were explored. In the first scenario the utility associated with LEN/DEX treatment was assumed to be the same as that for BTZ/DEX, whereas in the second scenario it was assumed to be the same as the utility value associated with the progression-free no treatment health state. The first scenario was considered for the base case analysis.

In the economic model mean values rather than median values were used despite the skewed distribution of the mapped utilities.

The overall mean value for the corresponding treatment group was used for the pre-progression on treatment states (ie. Health State A; pre-progression: PANO/BTZ/DEX and ‘pre-progression: LEN/DEX). These were thus 0.679 and 0.716, respectively for ‘pre-progression: PANO/BTZ/DEX’ and ‘pre-progression: LEN/DEX.

Acaster et al[24] report that HRQL improves when patients come off treatment compared to when they were on treatment (prior to stopping therapy, see section 3.2 in the main submission dossier). Furthermore, when off treatment patients do not experience the adverse events associated with active treatment. Thus utility values for the pre-progression, No treatment health state can be assumed to be higher than for the pre-progression, on treatment health states. In PANORAMA-1, HRQL was not measured in patients who discontinued treatment (for example due to adverse events or disease progression) or after completion of treatment (see section 5.4.1 in the main submission dossier). Therefore, the utility value associated with the treatment–free interval as published in Acaster et al.[24] was used (0.72). Acaster et al. conducted a cross-sectional postal survey in the UK. The survey was sent to 605 MM patients via the charity Myeloma UK and asked patients to rate their HRQL using the QLQ-C30, EORTC QLQ-MY20 and the EQ-5D measures.

No HRQL data from PANORAMA-1 was available for the post-progression health state. Instead, utility values published by van Agthoven et al[25] were used to derive values for the post-progression health state corresponding to 'Post progression, other treatments' (LLoT). Following previous health economic models submitted to NICE;[5,15] 0.64 was adopted for both post-progression health states. The utility value associated with death was assumed to be zero. Table 14 summarises the utility values used in the model.

Table 14. Utility values applied in the indirect treatment comparison: after prior IMiD and prior bortezomib and ≥ 2 prior lines of treatment

Health state	Utility (SD)
Pre-progression, Tx1 (PANO/BTZ/DEX)	0.679 (0.182)
Pre-progression, Tx1 (LEN/DEX)*	0.716 (0.201)
Pre-progression, no Tx1	0.720 (0.200)[a]
Post-progression	0.640 (0.128)[b]
Dead	0

[a] Assumed equal to corresponding BTZ+DEX utility value

[b] Standard error, assumed to be 20% of the mean value.

BTZ, bortezomib; DEX, dexamethasone; IMiD, immunomodulatory drug; LEN, lenalidomide; PANO, panobinostat; SD, standard deviation; Tx, treatment.

1.4.3 Health-related quality-of-life studies

For the detailed description of the results of the systematic review performed, please see section 5.4.3 in the main submission dossier.

Interpretation of the findings

The only published utility values for patients with MM are those published by van Agthoven et al 2004[25] which relate to patients receiving first-line therapy and those published by Acaster et al[24] which related to different stages of treatment. The pre-progression utility value reported by van Agthoven et al for patients receiving chemotherapy, 0.81, is higher than the values of 0.679 and 0.716 used here in the economic evaluation for 'pre-progression, on Tx1' health state. This is as expected given that the van Agthoven et al data relate to patients receiving first-line therapy. The utility value used in the economic model for the post-progression health state (0.64) is the calculated value by van Agthoven et al also applied in previous rrMM NICE appraisals. Van Agthoven et al do not report a utility value for pre-progression off-treatment though

Acaster et al[24] reports utility values for first-line therapy (0.63), treatment free remission followed by first line therapy (0.72), second-line therapy (0.67) and later disease (0.63). These values indicate an improvement of 0.09 points associated with treatment-free remission following first-line therapy in comparison with improvements of 0.041 and 0.004 for PANO/BTZ/DEX and LEN/DEX, respectively, used in the economic model. The smaller magnitude of experienced improvement in the model is consistent with the later stage in the treatment pathway (ie patients in the model are not newly-diagnosed). Acaster et al report a value of 0.63 for later stage disease which is lower than is used in the economic model for PANO/BTZ/DEX (0.679) and LEN/DEX (0.716).

1.4.4 Adverse reactions

Data from PANORAMA-1 indicate that HRQL during treatment with PANO/BTZ/DEX is lower than that in patients receiving LEN/DEX (see Table 13), presumably reflecting the increased incidence of adverse events (see section 4.12 in the main submission dossier). This is reflected in the model by the use of a lower utility value for the pre-progression health state associated with treatment with PANO/BTZ/DEX compared with that for BTZ/DEX (see Table 14).

1.4.5 Health-related quality-of-life data used in cost-effectiveness analysis

As demonstrated in two papers identified in a systematic review (see 1.4.3), HRQL in patients with MM varies according to stage of treatment and response to treatment. A cross-sectional survey of patients with MM found that HRQL is highest for patients in treatment-free remission and is lower in patients receiving treatment and in patients with later stages of disease.[24] A further study has reported an improved HRQL in patients in remission or who were asymptomatic compared with those receiving treatment,[26] and an analysis of data from a trial of bortezomib monotherapy has revealed an improvement in certain aspects of HRQL and symptoms in patients achieving at least a partial response (PR) compared with those with progressive disease.[27]

The health states in the model capture the impact of treatment, the treatment-free interval between treatments, and later lines of therapy on HRQL. HRQL is assumed to be constant within each health state, and the mean HRQL measured throughout the model corresponds to that for the pre-progression on treatment health states.

Table 15 summarises the utility values used in the model. Values for the pre-progression on treatment health states and pre-progression off treatment health state are derived from data from the pivotal phase 3 trial (which compared PANO/BTZ/DEX and BTZ/DEX) using a mapping algorithm, as described earlier. This approach is recommended by NICE when EQ-5D data are not available. The mapping section includes discussion of the identification of possible mapping functions that have been used to map from the EORTC QLQ-C30 or EORTC QLQ-MY20 to EQ-5D together with the rationale for the mapping function chosen for this analysis. No data from PANORAMA-1 were available to derive utility values for the comparator treatment (LEN/DEX) or the post-progression health state. Instead, in case of the comparator treatment, assumption was made the utility value would be equal with that of the BTZ/DEX in the PANORAMA-1 trial, while the utilities value published by van Agthoven et al[25] (see section 1.4.3) was used for the post-progression state corresponding to LLoT. The utility value associated with death was assumed to be zero.

Table 15. Summary of quality-of-life values for cost-effectiveness analysis: full population

State	Utility value, mean	Confidence interval, SD	Reference in submission	Justification
A: Pre-progression, Tx1 (PANO/BTZ/DEX)	0.679	0.182	Mapping	Derived using mapping from trial data
A: Pre-progression, Tx1 (LEN/DEX	0.716	0.201	Mapping	Derived using mapping from trial data
B: Pre-progression, No Tx1	0.720	0.200	Acaster et al, 2013	Based on off treatment value published by Acaster et al. assumed to equal the mean mapped utility value measured at the last treatment cycle
C and D: Post-progression, (LLoT)	0.64	0.128[a]	van Agthoven et al 2004	Based on post-progression value published by van Agthoven et al 2004
Dead	0	0		

[a] Standard error, assumed to be 20% of the mean value.

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; LLoT, last line of treatment; PANO, panobinostat; SD, standard deviation,

1.5 Cost and healthcare resource use identification, measurement and valuation

1.5.1 Resource identification, measurement and valuation studies

Costs used within the model reflect the UK health service perspective and consisted of five components:

- Drug acquisition costs
- Drug administration costs
- Treatment monitoring cost
- Costs for management of adverse events
- Terminal care costs

No formal literature searches were performed to identify resource use or health care costs. Drug acquisition costs were taken from the British National Formulary (BNF) and administration costs for bortezomib were assumed to correspond to the costs of a nurse visit. (All other treatments require oral administration and therefore no administration costs were included.) The tests performed and the frequency of monitoring during treatment were based on the assessments performed in the PANORAMA-1 study and were modified based on expert clinical opinion to reflect routine clinical practice in the UK. Costs of tests were taken from the National schedule of reference costs together with other publishes sources. Costs for management of adverse events were taken from the latest NICE reference cost document, sources used in previous NICE submissions and published literature. Costs for terminal care were taken from the National Audit Office (2008).[28]

1.5.2 Intervention and comparators' costs and resource use

Drug acquisition (and administration) costs

Drug acquisition costs were based on the most recent available list price and were extracted from the BNF (see Table 16) and the price for the panobinostat 20 mg tablet was assumed to be £776. Bortezomib is dosed per body surface area. The average body surface area was estimated to be 1.82 m^2, derived using a published formula[29] and utilizing the average weight (72 kg) and height (164 cm) of patients in the PANORAMA-1 trial. Table 16 summarises the unit cost and cost per administration for each drug.

Table 16. Unit cost and cost per administration for each drug

Drug	Unit	Unit cost	Dose	Cost/ dose	Source
Panobinostat*	20 mg	£776.00	20 mg	£776.00	Assumption
Bortezomib	3.5 mg	£762.38	1.3 mg/m^2	£512.54	BNF
Dexamethasone	2 mg	£0.78	20/40 mg	£7.80/ £15.6	BNF
Lenalidomide	25 mg	£208.00	25 mg	£208.00	BNF
Doxorubicin	30 ml	£18.72	30 mg/m^2	£102.21	BNF
Thalidomide	200 mg	£42.64	200 mg	£42.64	BNF
Cyclophosphamide	50 mg/300 mg	£0.82/£4.92	50 mg/300 mg	£0.82/£4.92	BNF
Pomalidomide	4 mg	£423.00	4 mg	£423.00	BNF

BNF, British National Formulary; [a] panobinostat price is based on assumption

Average drug costs per cycle were calculated for each regimen. As the PANO/BTZ/DEX and BTZ/DEX regimens are given as 3-weekly cycles, cost for other regimens were transformed to costs per 3-week cycle.

Treatment interruptions and subsequent dose reductions were allowed in the PANORAMA-1 trial. The average cost per cycle for PANO/BTZ/DEX was calculated based on the mean dose intensity in PANORAMA-1 (see Table 17) [22]. The average cycle cost was £5,375 in the first treatment phase[23] and £4,566 in the second treatment phase for PANO/BTZ/DEX.

In addition, the costs of drug administration were included for bortezomib. It was assumed that bortezomib is administered intravenously in all patients, as in the PANORAMA-1 clinical trial. Scenario analysis was performed for subcutaneous use. The cost associated with intravenous administration (£156) of bortezomib was assumed to be equal to the adult follow-up outpatient mandatory tariff price for speciality 303 Haematology [clinical] taken from the UK National Tariff 2013–2014. All other drugs are administered orally and were assumed to incur no administration costs. The cost associated with subcutaneous administration was assumed to equal the cost of a nurse visit (ie £25.00).

Table 17. Mean dose intensity in the PANORAMA-1 trial

	Panobinostat	Bortezomib	Dexamethasone
PANO/BTZ/DEX	80.7%	75.8%	87.5%

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

[22] At the time of the submission, no data on dose intensity in the restricted population was available therefore it was assumed that the dose intensity observed in the full trial population would be applicable to the restricted population.

[23] Bortezomib is given only once weekly and dexamethasone only four times weekly from cycle 8 per the clinical trial protocol and the anticipated licence

The cost of lenalidomide applied in the model was calculated as a weighted average of daily doses across all patient days in the MM-010 study. The cost of concomitant use of granulocyte colony-stimulating factor (G-CSF) was also included[24] in the cost of lenalidomide by assuming all patients received G-CSF after their first dose interruption. The resulting weighted average 28 days cycle cost for lenalidomide was £3,773 as published in the Single Technology Appraisal (STA) of lenalidomide for the treatment of MM in people who have received at least one prior therapy with bortezomib (TA171[5]).[5] This average cycle cost was transformed into a 3-weekly cycle cost of £2,830. Because the manufacturer of lenalidomide has agreed a patient access scheme (PAS) with the Department of Health, in which the cost of lenalidomide for people who remain on treatment for more than 26 cycles (each of 28 days) is met by the manufacturer, in the model lenalidomide costs were only applied for 35 (ie ≈26*28/21) 3-weekly cycles. The cost for dexamethasone was £2.59 per 28-day cycle (ie £1.94 per 3-weekly cycle).

As with lenalidomide, the cost of pomalidomide applied in the model took into account dose interruptions. Depending on the treatment cycle, the estimated 28-day cycle cost varied between £7,375.09 and £8,884.00, as published in the STA of pomalidomide for relapsed and refractory MM.[8] For the economic model, the average of these costs was taken (ie £8,130) and was transformed into an average 3-weekly cycle cost (ie £6,097). The cost of dexamethasone was £2.17 per cycle (ie £1.63 per 3-weekly cycle). The cost of concomitant[8] medications was included and estimated to be £22.63 per week (ie £67.89 per 3-weekly cycle).

Treatment costs for LLoT − beyond the costs associated to POM/DEX − were obtained from the study of Gooding et al[13] which was assumed to represent the typical treatment costs after third-line treatment in the UK. This study reported treatments given and further supportive care, ie MRU costs for a cohort of double-refractory/intolerant patients with MM in the UK. Data on anti-myeloma therapies prescribed and MRU were obtained from a single centre in Oxford for 36 patients who had received four lines of treatment between 2011 and 2013. Median age at diagnosis for the cohort was 65.3 years (48 to 83 years). MRU (clinic attendance, inpatient admissions, supportive therapies, transfusions and blood tests) from start of fourth-line therapy until death or to the last follow-up were retrieved from health care records. When offered a choice of therapy, 77% of patients preferred an active treatment to care with palliative intent. Therapies were typically bendamustine-based regimens (53%), retreatment with bortezomib (10%) or lenalidomide -based regimens (27%). Patients received treatment for a mean of 15.3 weeks. The mean drug cost for fourth-line anti-MM therapy – excluding POM/DEX, which was not yet available at the time of the study – was £5,101 per patient (ie £1,001 per 3-weekly cycle), and the mean MRU cost during fourth-line therapy was £11,160 (ie £2,188 per 3-weekly cycle). For the purpose of the model, the average 3-weekly cost for supportive care was assumed to correspond to the average 3-weekly MRU cost.

[24] Concomitant use of granulocyte colony-stimulating factor (G-CSF) was applied by assuming all patients received lenalidomide, 2 5mg, with G-CSF after their first dose interruption (26.8% of the patients, £473.62 per patient 4-weekly cycle cost, i.e. £95 per 3-weekly cycle).

The proportion of patients receiving any type of active treatment is assumed to be 77% in line with Gooding et al, of which 31.5 receive POM/DEX and 45.5% receive other active treatment as described by Gooding et al. The average 3 weekly cycle cost is derived from these treatments and equals with £4,586.

Table 18. Costs per 3-week cycle for regimens included in the model

Regimen	Cost per 3-week cycle	Comments
PAN/BTZ/DEX[a]	£5,375 (first treatment phase, cycles 1 to 8) £4,566 (second treatment phase, cycles 9 to 16)	IV administration cost of £156 per treatment to be added for BTZ
LEN	£2,830	Applied for 35 3-weekly cycles Cost of DEX, £1.94 per cycle and G-CSF, £95 per 3-week cycle to be added
POM	£6,097	Cost of DEX, £1.63 per cycle and concomitant medications, £67.89 per cycle, to be added
Fourth-line therapy (other active treatments)	£1,001	Gooding et al.[13]
MRU	£2,188	Gooding et al.[13]

BTZ, bortezomib; DEX, dexamethasone; G-CSF, granulocyte colony-stimulating factor; IV, intravenous; LEN, lenalidomide; MRU, medical-resource utilisation; PANO, panobinostat; POM, pomalidomide.

[a]Based on assumption.

Treatment monitoring costs

Monitoring costs were applied in the model for patients being in the pre-progression health states (ie pre-progression, Tx1 and pre-progression, no Tx) but not for post-progression treatment (ie. third- and fourth-line) as a simplifying assumption. The treatment monitoring scheme used was adapted from the visit schedule and assessments scheme used by participating physicians in the PANORAMA-1 trial (see Table 19). The adapted scheme was validated by a clinical expert. This monitoring scheme was used to calculate average monitoring costs per 3-week cycle based on the unit costs summarised in Table 20. Monitoring costs were assumed to be the same for both PANO/BTZ/DEX and BTZ/DEX and estimated to be £171. Based on expert opinion, it was assumed that pre-progression patients who were not on treatment would receive regular monitoring on a 6-weekly basis, hence the average monitoring cost calculated per cycle was half of that applied while on treatment.

Table 19. Monitoring scheme for pre-progression therapy (PANO/BTZ/DEX or BTZ/DEX)

Activity	Frequency per cycle
Serum protein assessment	1.00
Skeletal survey (bone X-ray)	0.23
Lab results – haematology	1.00
Lab results – thyroid function test	1.00
Lab results – blood chemistry	1.00
Specialist visit	0.06

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

Table 20. Unit costs per monitoring activity

Activity	Unit cost	Source
Serum protein assessment	£15	NICE TA338, Pomalidomide
Skeletal survey (bone X-ray)	£75.00	2014, http://www.nice.org.uk/guidance/cg176/resources/cg176-head-injury-costing-template2
Lab results - Haematology	£3.00	2014, Directly Accessed Pathology Services, Haematology, National schedule of reference costs (2013-2014)
Lab results - Thyroid function test	£18.00	2014, http://www.nice.org.uk/guidance/ta312/resources/ta312-multiple-sclerosis-relapsingremitting-alemtuzumab-costing-template2
Lab results - Blood chemistry	£3.00	2014, Directly Accessed Pathology Services, Haematology, National schedule of reference costs (2013-2014)
Specialist visit	£156.00	2014, Outpatients - Consultant Led, Clinical haematology, National schedule of reference costs (2013-2014)

NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

Treatment monitoring costs – LEN/DEX

Monitoring costs for LEN/DEX was taken from the STA of lenalidomide for the treatment of MM in people who have received at least one prior therapy with bortezomib (NICE TA171)[5]. The 4-weekly monitoring cost was rescaled to 3-weekly monitoring costs resulting in £146 per cycle.

1.5.3 Health-state unit costs and resource use

Table 21. List of health states and associated costs in the economic model

Health states	Items	Value	Reference in submission
Pre-progression, Tx1	PANO/BTZ/DEX[a]	£5,366 (first treatment phase, cycles 1 to 8) £4,562 (second treatment phase, cycles 9 to 16)	Section 1.5.2
	LEN/DEX	£2,831.69	Section 1.5.2
	Concomitant med. to LEN/DEX	£95.20	Section 1.5.2
	IV administration	£156	Section 1.5.2
	Monitoring and tests	£185.56	Section 1.5.2
	Adverse events	PANO/BTZ/DEX: £136.85	Section 1.5.4
	Total (PANO/BTZ/DEX)	£6,293 (cycle 1 to 8) £5,176 (cycle 9 to 16)	
	Total (LEN/DEX)	£2,926.89	
Pre-progression, no Tx1	Monitoring costs	£185.56 / 2 = £92.78	Section 1.5.2
Post-progression other treatments	POM/DEX Concomitant med.	£6098.63 £67.89	Section 1.5.2
	Other active treatments	£1,001	Section 1.5.2
	MRU	£2,188	Section 1.5.2
Death	Terminal care	£1,235 lump sum applied on death	Section 1.5.5

[a] Based on assumption.

BTZ, bortezomib; DEX, dexamethasone; IV, intravenous; LEN, lenalidomide; MRU, medical-resource utilisation; PANO, panobinostat; POM, pomalidomide.

1.5.4 Adverse reaction unit costs and resource use

Costs for management of adverse events were applied in the model to patients receiving pre-progression treatment (ie PANO/BTZ/DEX or LEN/DEX) but not for post-progression treatment (ie PANO/DEX or BSC). Estimated 3-weekly costs were either determined from adverse event occurrence probabilities and management costs for the ten most frequently occurring grade 3/4 adverse events reported in PANORAMA-1 population with at least two prior lines of treatment including an IMiD and bortezomib, or based on NICE TA171.[5]

For patients who progressed (ie in the 'post-progression' health state) no adverse event costs were applied in the model assuming the MRU cost absorbs it and for simplicity reasons.[13]

Adverse event costs – PANO/BTZ/DEX

Daily adverse event occurrence rates in patients receiving PANO/BTZ/DEX were estimated as the number of patients for whom grade 3/4 adverse events were documented divided by the total treatment exposure time expressed in patient-days[25] (see Table 22). The daily adverse event rates were then transformed into 3-weekly occurrence rates by multiplying daily rates by 21, and subsequently into 3-weekly probabilies by transforming rates into probabilities (probability = 1 – exp(-rate).

Table 22. Adverse events observed in the prior IMiD and prior bortezomib and ≥ 2 prior lines of treatment trial population (safety set)[26]

PANO/BTZ/DEX (n = 72)		
Mean study treatment exposure, days	180.7	
Total exposure time to treatment, patient-days	13,008	
Grade 3/4 AEs	**N**	**3-weekly occurrence probability**
Anaemia	16	0.025
Asthenia	6	0.010
Diarrhoea	24	0.038
Fatigue	16	0.025
Hypokalaemia	15	0.024
Hyponatraemia	5	0.008
Lymphopenia	9	0.014
Neutropenia	23	0.036
Pneumonia	10	0.016
Thrombocytopenia	43	0.067

AEs, adverse events; BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

Management costs of the ten most frequently reported grade 3/4 adverse events were obtained from various sources including the latest NICE reference cost document, previous NICE submission dossiers, or published literature. These are presented in Table 23. Only direct costs were taken into account and no differentiation was made between inpatient and outpatient management costs.

[25] Occurrence rate = number of incident cases / treatment exposure time (days).

[26] Safety set = patients who received at least one dose of study treatment

Table 23. Costs per adverse event

Grade 3 and 4 adverse events	Unit cost	Source
Anaemia	£1,155	2014, Non-Elective Inpatients - Long Stay, Iron Deficiency Anaemia (SA04L), National schedule of reference costs (2013–2014)[30]
Asthenia	£12	2013, TA316
Diarrhoea	£623	2013, TA316
Fatigue	£12	2013, TA316
Hypokalaemia	£355	2014, High Cost Drugs, Intravenous Nutrition, Band 1 (XD26Z), National schedule of reference costs (2013–2014)[30]
Hyponatraemia	£355	Assumed to be the same as Hypokalaemia
Lymphopenia	£167	Assumed to be the same as Neutropenia
Neutropenia	£167	2014, High Cost Drugs, Neutropenia Drugs, Band 1 (XD25Z), National schedule of reference costs (2013–2014)[30]
Pneumonia	£1,433	2014, Non-Elective Inpatients - Long Stay, Atypical or Viral Pneumonia (DZ11J), National schedule of reference costs (2013–2014)[30]
Thrombocytopenia	£604	2013, Non-Elective Inpatients - Short Stay, Thrombocytopenia (SA12K), National schedule of reference costs (2013–2014)[30]

To estimate the 3-weekly adverse event costs for PANO/BTZ/DEX and BTZ/DEX, the cost for each adverse event was multiplied by the corresponding 3-weekly adverse event occurrence probability and the total was derived by summing the 3-weekly costs for each of the ten adverse events. The resulting overall costs (£136.85 for PANO/BTZ/DEX) were applied in every 3-week cycle of the treatment period of the model for patients who received PANO/BTZ/DEX treatment.

Adverse event costs – LEN/DEX

Adverse event costs for LEN/DEX was taken from the STA of lenalidomide for the treatment of MM in people who have received at least one prior therapy with bortezomib (TA171).[5] The 4-weekly monitoring costs (£17.11 per 4 weeks) was rescaled to 3-weekly adverse event costs resulting in £12.83 per cycle.

1.5.5 Miscellaneous unit costs and resource use

Terminal care costs

A one-off terminal care cost of £1,235 is applied in the model when a patient dies adopting the calculations published in the single technology appraisal of lenalidomide for relapsed and refractory MM (NICE TA171).[5] Costs of terminal care in the UK have been estimated to be £6,177. For the

purpose of the model, it was assumed that 20% of the patients that die actually receive terminal care (ie it is assumed that 20% of patients use hospital services).

1.6 Summary of base-case de novo analysis inputs and assumptions

1.6.1 Summary of base-case de novo analysis inputs

Table 24 summarises the variables used in the analysis.

Table 24. Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
PANO/BTZ/DEX			
Risk of progression or death, *constant*	–3.956 (Figure 3)	–4.933 to –2.979, MVN	Section 1.3.2
Risk of progression or death, ln(*P)*	0.302 (Figure 3)	0.069 to 0.534, MVN	Section 1.3.2
Risk of treatment discontinuation, *constant*	–2.377(Figure 4)	–2.639 to -2.115, Normal	Section 1.3.2
Risk of death, constant	–4.302 (**Error! Reference source not found.**)	–4.925 to -3.678, MVN	Section 1.3.2
Risk of death, Gamma	0.015 (**Error! Reference source not found.**)	–0.011 to 0.042, MVN	Section 1.3.2
LEN/DEX hazard ratio			
Risk of progression or death, ln(*HR)* *(unadjusted Cox model, 2 prior LOT)*	0.059 (Section 1.3.3)	–0.226 to 0.344	Section 1.3.3
Risk of progression or death, ln(*HR)* *(MAIC, ITT)*	0.002 (Section 1.3.3)	–0.224 to 0.248	Section 1.3.3
Risk of treatment discontinuation, *HR (median PFS / median duration for LEN/DEX)*	0.094 (Section 1.3.3)	0.057 to 0.131	Section 1.3.3
Risk of death, ln(*HR)* *(unadjusted Cox model, 2 prior LOT)*	0.072 (Section 1.3.3)	–0.278 to 0.422	Section 1.3.3
Risk of death, ln(*HR)* *(MAIC, ITT)*	0.050 (Section 1.3.3)	–0.257 to 0.358	Section 1.3.3
Adverse events (PANO/BTZ/DEX)			
Anaemia, %	0.026 (**Error! Reference source not found.**)	0.008 to 0.054, beta	Section 1.5.4
Asthenia, %	0.010 (**Error! Reference source not found.**)	0.003 to 0.020, beta	Section 1.5.4
Diarrhoea, %	0.039 (**Error! Reference source not**	0.011 to 0.080, beta	Section 1.5.4

	found.)		
Fatigue, %	0.026 (**Error! Reference source not found.**)	0.008 to 0.054, beta	Section 1.5.4
Hypokalaemia, %	0.024 (**Error! Reference source not found.**)	0.007 to 0.050, beta	Section 1.5.4
Hyponatraemia, %	0.008 (**Error! Reference source not found.**)	0.002 to 0.017, beta	Section 1.5.4
Lymphopenia, %	0.015 (**Error! Reference source not found.**)	0.004 to 0.030, beta	Section 1.5.4
Neutropenia, %	0.037 (**Error! Reference source not found.**)	0.011 to 0.077, beta	Section 1.5.4
Pneumonia, %	0.016 (**Error! Reference source not found.**)	0.005 to 0.034, beta	Section 1.5.4
Thrombocytopenia, %	0.069 (**Error! Reference source not found.**)	0.019 to 0.142, beta	Section 1.5.4
Utilities (3-weekly)			
Pre-progression, PANO/BTZ/DEX	0.039 (Table 14)	0.038 to 0.040, beta	Section 1.4.5
Pre-progression, LEN/DEX	0.041 (Table 14)	0.040 to 0.042, beta	Section 1.4.5
Post-progression, Further treatments	0.037 (Table 14)	0.036 to 0.038, beta	Section 1.4.5
Pre-progression, no treatment	0.042 (Table 14)	0.038 to 0.045, beta	Section 1.4.5
Costs			
Administration: LEN/DEX only, first cycle only	£166 (**Error! Reference source not found.**)	£108 to £234, gamma	Section 1.5.2
Concomitant G-CSF: LEN/DEX only	£95 (**Error! Reference source not found.**)	£62 to £136, gamma	Section 1.5.2
Monitoring & tests: LEN/DEX (cycle 1 to 2)	£636 (**Error! Reference source not found.**)	£411 to £908, gamma	Section 1.5.2
Monitoring & tests: LEN/DEX (cycle 3+)	£135 (**Error! Reference source not found.**)	£87 to £193, gamma	Section 1.5.2
AE costs, LEN/DEX	£13 (**Error! Reference source not found.**)	£8 to £18, gamma	Section 1.5.2
Intravenous administration of BTZ	£156 (**Error! Reference source not found.**)	£101 to £223, gamma	Section 1.5.2

Serum protein assessment	£15 (Table 20)	£10 to £22, gamma	Section 1.5.2
Skeletal survey (bone X-ray)	£75 (Table 20)	£49 to £107, gamma	Section 1.5.2
Lab results – haematology	£3 (Table 20)	£2 to £4, gamma	Section 1.5.2
Lab results – thyroid function test	£18 (Table 20)	£12 to £26, gamma	Section 1.5.2
Lab results – blood chemistry	£3 (Table 20)	£2 to £4, gamma	Section 1.5.2
Visit	£156 (Table 20)	£101 to £223, gamma	Section 1.5.2
Anaemia	£1,155 (Table 23)	£748 to £1650, gamma	Section 1.5.4
Asthenia	£12 (Table 23)	£8 to £81, gamma	Section 1.5.4
Diarrhoea	£623 (Table 23)	£403 to £890, gamma	Section 1.5.4
Fatigue	£12 (Table 23)	£8 to £18, gamma	Section 1.5.4
Hypokalaemia	£355 (Table 23)	£230 to £507, gamma	Section 1.5.4
Hyponatraemia	£355 (Table 23)	£230 to £507, gamma	Section 1.5.4
Lymphopenia	£167 (Table 23)	£108 to £239, gamma	Section 1.5.4
Neutropenia	£167 (Table 23)	£108 to £239, gamma	Section 1.5.4
Pneumonia	£1,433 (Table 23)	£927 to £2046, gamma	Section 1.5.4
Thrombocytopenia	£604 (Table 23)	£391 to £862, gamma	Section 1.5.4
Terminal care	£1,235 (section 1.5.5)	£799 to £1765, gamma	Section 1.5.5

AE, adverse event; BTZ, bortezomib; DEX, dexamethasone; CI, confidence interval, G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; ITT, intention-to-treat; IV, intravenous; LEN, lenalidomide; LOT, line of treatment; MAIC, matching adjusted indirect treatment comparison; MVN, multivariate normal; PANO, panobinostat; TTP, time to progression

1.6.2 Assumptions

The key assumptions of used in the model and their justification are summarised in Table 25.

Table 25. Key assumptions used in the model and their justification

Assumption	Justification
1) patients experiencing progression on PANO/BTZ/DEX or LEN/DEX receive POM/DEX or BSC until they die; the relative frequency of the post-progression treatments was assumed to correspond to those reported by Gooding et al[13] as well as assumption made on POM/DEX	POM/DEX is approved[31] for treatment of patients who have received at least two prior treatment regimens, including both LEN and BTZ, and have demonstrated disease progression on the last therapy. POM/DEX is available and covered by CDF Gooding et al presents costs for fourth-line therapy in a single UK centre between 2011 and 2013 and is believed to be representative of current fourth-line therapy in England and Wales
2) Costs associated with fourth-line treatment other than POM/DEX were assumed to correspond to those reported by Gooding et al,[13] a study of fourth-line therapy in a single UK centre[13]	Gooding et al presents costs for fourth-line therapy in a single UK centre between 2011 and 2013 and is believed to be representative of current fourth-line therapy in England and Wales
3) Terminal care cost is assumed for 20% of the patients who die.	This assumption is in line with the assumption on other recent rrMM NICE appraisals.
4) Mortality risk is applied exclusively from the trial. No distinction is made between mortality related to MM or unrelated to MM.	Given the short life expectancy of patients with rrMM, only trial data were used to model the OS of patients, i.e. no general population mortality was considered additionally.
5) BTZ as part of PANO/BTZ/DEX is assumed to be administered intravenously	Reflecting use in PANORAMA-1 clinical trial and current clinical practice.
6) More frequent monitoring activity is required while on treatment than during the treatment free interval.	Clinical expert opinion advised that less frequent monitoring is used when off treatment
7) HRQL for patients in the Pre-progression, No treatment health state is assumed to be equal to that of patients during the last cycle of pre-progression treatment (ie cycle 16 for PANO/BTZ/DEX or BTZ/DEX).	The value used is higher than the mean for the overall treatment phase as expected given that HRQL has been shown to be better when off treatment[24]

BSC, best supportive care; BTZ, bortezomib; CDF, Cancer Drugs Fund; DEX, dexamethasone; HRQL, health-related quality of life; LEN, lenalidomide; NICE, National Institute for Health and Care Excellence; MM, multiple myeloma; OS, overall survival; PANO, panobinostat; POM, pomalidomide; rrMM, relapsed and /or refractory multiple myeloma

1.7 Results

Results are presented for all four/three methodologies applied to derive the related cost-effectiveness results for the restricted patient population, ie patients with at least two prior lines of treatments including an IMiD and bortezomib.

In order to derive the HRs the following methodologies were applied as discussed in section 1.3.2 and 1.3.3.

The four methods applied on the full trial population[27] are the 'Common comparator' (Common) method, the 'Naïve indirect treatment comparison' (Naïve) method, the Unadjusted Cox method (Cox) and the 'Matching adjusted indirect treatment comparison' (MAIC) method. Three of the above methods – with the exception being the common comparator method – were also applied on the other available dataset, the subpopulation with 2 to 3 lines of prior treatment.

The above choice is based on the following arguments:

1. MAIC attempts to take baseline characteristics into consideration which are important
    a. Clinicians suggest that the one of the most relevant factors regarding the choice of therapy for patients with rrMM is the mechanism of action.
    b. Also it is seen in the HMRN research32 that, while certain factors don't seem to influence survival, such as sex, other characteristics have a huge influence on it, such as age at diagnosis, the type of the first line treatment and most of all the accessibility to prior ASCT, which is closely related to age and general condition at diagnosis.
2. On bigger sample sizes, such as the full population, MAIC works well since it doesn't assign extreme weights to patients with certain characteristics that may distort the comparison. However this is also its biggest disadvantage, hence it is not a good choice for the smaller subpopulation with 2 to 3 prior lines of treatment because it increases its reliability on minor patient pools.
3. Beyond the MAIC method, the Unadjusted Cox allows the exclusion of patients with certain criteria having high importance, eg the prior use of LEN/DEX in this case. By using unadjusted Cox in the restricted pool, we are still able to rule out the patient with prior LEN/DEX, yet keep the patient number effectively high to generate reliable results.

Table 26 summarises the HRs for LEN/DEX versus PANO/BTZ/DEX assumed to be applicable for the targeted population with at least two prior lines of treatment including an IMiD and bortezomib. As summarised in Table 12, each method has its advantages and disadvantages. For the analysis presented here we suggest the following two methodologies provide the most appropriate approach for deriving the relative efficacies of the PANO/BTZ/DEX versus LEN/DEX for use in the economic evaluation:

- the 'MAIC' methodology deriving HR based on the full populations[10,17]
- the 'Unadjusted Cox' method on the subpopulation with 2 to 3 prior lines of treatment[9]

[27] Please note that in case of PANORAMA-1, patients with prior lenalidomide based regimen were excluded.

The various sensitivity analyses will be performed applying the latter method only. Nonetheless for acquiring a fuller picture, the results regarding costs, LYs and QALYs gained as well as ICERs will be presented for both of the two most plausible methods.

The above choice is based on the following arguments:

4. MAIC attempts to take baseline characteristics into consideration which are important
    a. Clinicians suggest that the one of the most relevant factors regarding the choice of therapy for patients with rrMM is the mechanism of action.
    b. Also it is seen in the HMRN research[32] that, while certain factors don't seem to influence survival, such as sex, other characteristics have a huge influence on it, such as age at diagnosis, the type of the first line treatment and most of all the accessibility to prior ASCT, which is closely related to age and general condition at diagnosis.
5. On bigger sample sizes, such as the full population, MAIC works well since it doesn't assign extreme weights to patients with certain characteristics that may distort the comparison. However this is also its biggest disadvantage, hence it is not a good choice for the smaller subpopulation with 2 to 3 prior lines of treatment because it increases its reliability on minor patient pools.
6. Beyond the MAIC method, the Unadjusted Cox allows the exclusion of patients with certain criteria having high importance, eg the prior use of LEN/DEX in this case. By using unadjusted Cox in the restricted pool, we are still able to rule out the patient with prior LEN/DEX, yet keep the patient number effectively high to generate reliable results.

Table 26. Summary of the hazard ratios for LEN/DEX versus PANO/BTZ/DEX obtained by the four/three different indirect treatment comparison methods as applied in this current full analysis

		PFS		OS	
		HR	SE	**HR**	SE
Full trial population based	Common comparator method[28]	**1.870**	0.356	**1.216**	0.384
	Naïve comparison[29]	**1.081**	0.216	**1.006**	0.201
	Unadjusted Cox[30]	**0.929**	0.104	**0.997**	0.131
	MAIC[31]	**1.002**	0.126	**1.052**	0.157

[28] For further information (population specific PFS and OS data) please see table 24 in the main submission dossier

[29] For further information (population specific PFS and OS data) please see table 25/a in the main submission dossier

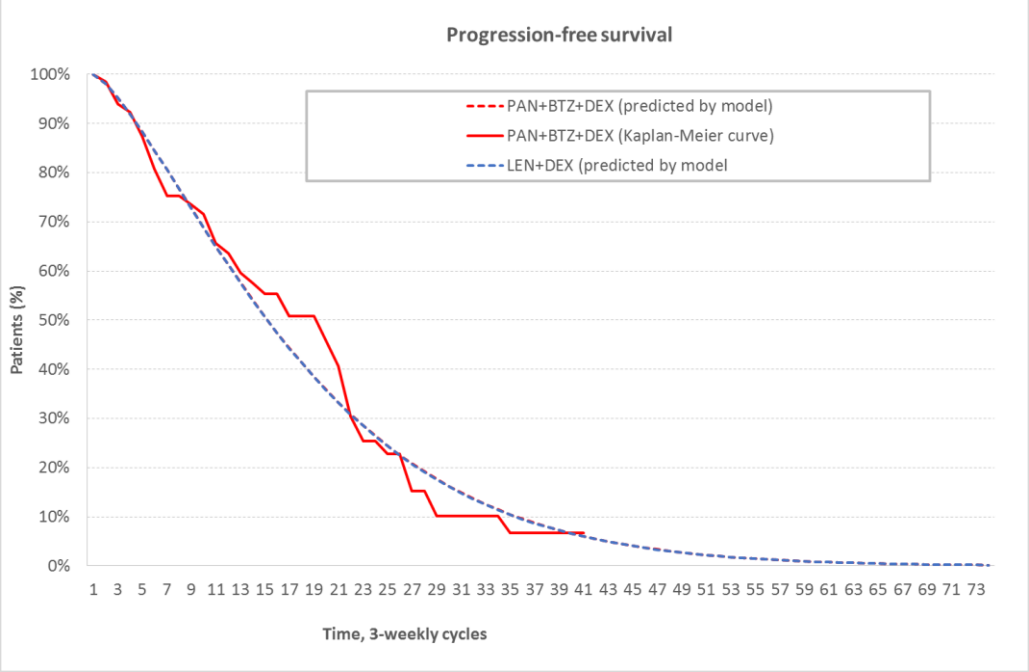
[30] For further information (population specific PFS and OS data) please see table 26/a in the main submission dossier

Based on the subpopulation with 2 to 3 lines of prior treatment	Naïve comparison[32]	**1.190**	0.238	**0.959**	0.192
	Unadjusted Cox[33]	**1.061**	0.145	**1.075**	0.179
	MAIC[34]	**1.108**	0.331	**1.413**	0.424

HR, hazard ratio; MAIC, matching adjusted indirect treatment comparison; OS, overall survival; PFS, progression-free survival; SE, standard error.

Figure 7. a) Progression-free survival and b) overall survival Kaplan–Meier curves derived for LEN/DEX and PANO/BTZ/DEX using the MAIC method for the full patient population

a)



[31] For further information (population specific PFS and OS data) please see table 28/a in the main submission dossier

[32] For further information (population specific PFS and OS data) please see table 25/b in the main submission dossier

[33] For further information (population specific PFS and OS data) please see table 26/b in the main submission dossier

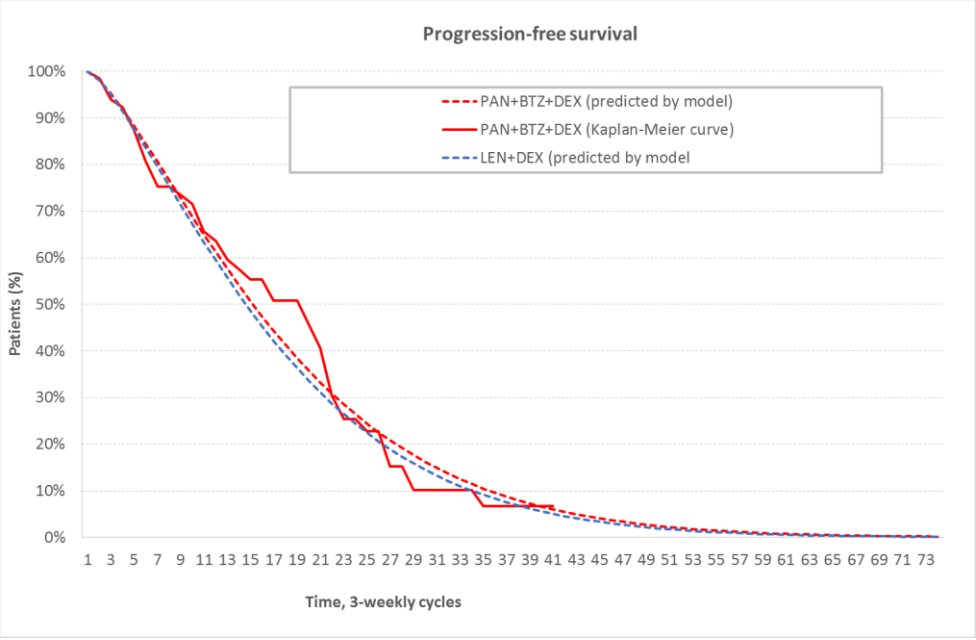
[34] For further information (population specific PFS and OS data) please see table 28/b in the main submission dossier

b)

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PAN(O), panobinostat.

Figure 8. a) Progression-free survival and b) overall survival Kaplan–Meier curves derived for LEN/DEX and PANO/BTZ/DEX using the Cox method for the prior 2 to 3 lines of treatment population

a)



b)

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PAN(O), panobinostat.

1.7.1 Incremental cost effectiveness analysis results

Although there are clear differences between the QALY gains using the base case methods, these are not particularly meaningful when considered in real terms: they range between 0.0295 and 0.0518, which converts to 8 days. Thus, the evidence suggests that one cannot distinguish between panobinostat and lenalidomide in this subpopulation in terms of efficacy and that the determining factor will be the cost of the PANO/BTZ/DEX combination. It should also be noted that, because of these small incremental QALYs, the ICERs are volatile and subject to switch from dominant to dominated quite easily, thus making interpretation more problematic.

Table 27. Results per the two most plausible methodologies applied (discounted) with two price scenarios

Base case: assuming £776 per 20 mg capsule

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per LYs gained[a]	ICER (£) Cost per QALYs gained[a]
'MAIC' deriving HRs from full trial populations	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.071	0.0295	£[redacted]	£[redacted]
	LEN/DEX	£148,567	2.216	1.491					
'Unadjusted Cox' deriving HRs from subpopulation (2 to 3 prior lines)	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.102	0.0518	£[redacted]	£[redacted]
	LEN/DEX	£147,632	2.186	1.469					

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LYG, life years gained; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; QALYs, quality-adjusted life years

1.7.2 Clinical outcomes from the model

Comparing the model results with the clinical outcomes of the PANO/BTZ/DEX combination treatment in the subpopulation with at least two prior lines of treatment including an IMiD and bortezomib reveals the following:

- The model slightly underestimates the median PFS by 0.5 months
- The model underestimates the median OS by 4.3 months
- The model overestimates the median treatment duration, hence the cost associated to PANO/BTZ/DEX combination treatment as well.

Table 28. Summary of model results compared with clinical data

Outcome	**Clinical trial result** (Prior IMiD, BTZ and ≥ 2 LoT)	**Model result**
Median PFS (PANO/BTZ/DEX)	12.5 months	12.0 months
Median OS (PANO/BTZ/DEX)	[redacted] months	26.2 months
Median treatment duration (PANO/BTZ/DEX)	4.2 months	5.5 months
Proportion of patients experiencing adverse events (PANO/BTZ/DEX)	Rates obtained from trial	Rates obtained from trial

BTZ, bortezomib; DEX, dexamethasone; IMiD, immunomodulatory drug; LoT, line of treatment; OS, overall survival; PANO, panobinostat; PFS, progression-free survival

1.7.3 Disaggregated results of the base case incremental cost effectiveness analysis

Tables below provide an overview of the undiscounted and discounted costs the model predicts for the patient populations for each health state applying the two most plausible methods.

'MAIC' deriving HRs from full trial populations

Table 29. Summary of QALY gain by health state using 'MAIC' and deriving HRs from full trial populations – discounted

Health state	QALY intervention (PANO/BTZ/DEX)	QALY comparator (LEN/DEX)	Increment	Absolute increment	% absolute increment
Pre-progression on treatment	0.33	0.64	–0.31	0.31	48%
Pre-progression off treatment	0.34	0.05	0.30	0.30	45%
Post progression	0.85	0.80	0.04	0.04	7%
Death	0	0	0.00	0.00	0%
Total	1.52	1.49	0.029	0.651	100%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; QALY, quality-adjusted life year.

Table 30. Summary of cost by health state using 'MAIC' and deriving HRs from full trial populations - discounted

Health state	Cost intervention (PANO/BTZ/DEX)	Cost comparator (LEN/DEX)	Increment	Absolute increment	% absolute increment
Pre-progression on treatment	£50,417	£47,380	£3,037	£3,037	33%
Pre-progression off treatment	£762	£101	£660	£660	7%
Post progression	£[redacted]	£99,944	£[redacted]	£[redacted]	[redacted]%
Death	£1,139	£1,142	-£3	£3	0%
Total	£[redacted]	£148,567	£[redacted]	£[redacted]	100%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat.

Table 31. Summary of predicted resource use by category of cost using 'MAIC' and deriving HRs from full trial populations – discounted

Item	Cost intervention (PANO/BTZ/DEX)	Cost comparator (LEN/DEX)	Increment	Absolute increment	% absolute increment
Drug costs	£46,381	£42,156	£4,225	£4,225	4225.061
Tests and monitoring (on treatment)	£2,882	£5,025	-£2,143	£2,143	2143.334
Tests and monitoring (No treatment)	£762	£101	£660	£660	660.2013
Last line of treatment	£[redacted]	£99,944	£[redacted]	£[redacted]	[redacted]
Adverse events	£1,155	£199	£955	£955	955.312
Terminal care	£1,139	£1,142	-£3	£3	3.03734
Total	£[redacted]	£148,567	£[redacted]	£[redacted]	100%

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat.

'Unadjusted Cox' deriving HRs from subpopulation (2 to 3 prior lines)

Table 32. Summary of QALY gain by health state using the 'Unadjusted Cox' method and deriving HRs from subpopulation (2 to 3 prior lines) – discounted

Health state	QALY intervention (PANO/BTZ/DEX)	QALY comparator (LEN/DEX)	Increment	Absolute increment	% absolute increment
Pre-progression on treatment	0.33	0.62	-0.29	0.29	46%
Pre-progression off treatment	0.34	0.04	0.30	0.30	48%
Post progression	0.85	0.81	0.04	0.04	6%
Death	0	0	0.00	0.00	0%
Total	1.52	1.47	0.052	0.622	100%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; PANO, panobinostat.

Table 33. Summary of cost by health state using the 'Unadjusted Cox' method and deriving HRs from subpopulation (2 to 3 prior lines) – discounted

Health state	Cost intervention (PANO/BTZ/DEX)	Cost comparator (LEN/DEX)	Increment	Absolute increment	% absolute increment
Pre-progression on treatment	£50,417	£45,794	£4,623	£4,623	45%
Pre-progression off treatment	£762	£97	£664	£664	7%
Post progression	£[redacted]	£100,598	£[redacted]	£[redacted]	[redacted]%
Death	£1,139	£1,143	-£4	£4	0%
Total	£[redacted]	£147,632	£[redacted]	£[redacted]	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; PANO, panobinostat.

Table 34. Summary of predicted resource use by category of cost using the 'Unadjusted Cox' method and deriving HRs from subpopulation (2 to 3 prior lines) – discounted

Item	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Drug costs	£46,381	£40,724	£5,657	£5,657	5656.95
Tests and monitoring (on treatment)	£2,882	£4,878	–£1,997	£1,997	1996.788
Tests and monitoring (No treatment)	£762	£97	£664	£664	664.1771
Last line of treatment	£[redacted]	£100,598	£[redacted]	£[redacted]	[redacted]
Adverse events	£1,155	£191	£963	£963	963.3237
Terminal care	£1,139	£1,143	-£4	£4	4.323211
Total	£[redacted]	£147,632	£[redacted]	£[redacted]	100%

HR, hazard ratio.

1.8 Sensitivity analyses

The economic model has numerous parameters which are integral to providing the model outcomes. To determine which parameters have the greatest impact on the model outcomes, further analyses are required. Hence, sensitivity analyses were used to investigate how sensitive a model is to changes from the deterministic input parameter values. Uncertainty margins were applied to each input parameter of interest based on corresponding margins provided in literature or based on assumptions if information was unavailable.

In particular, the cost-effectiveness model accommodated three different ways of assessing the impact of input parameter uncertainty on the model outcomes. These included deterministic (or univariate) sensitivity analyses, probabilistic sensitivity analyses, and scenario analyses:

- Deterministic sensitivity analyses were used to determine the drivers of the model outcomes;
- Probabilistic sensitivity analysis were used to display how the combined uncertainty of all input parameters translates into the overall uncertainty of the model outcomes;
- Scenario analyses were used to assess the impact of certain model settings on the results that were not subject to the deterministic sensitivity analyses (eg time horizon of the model, alternative input parameter choices).

The deterministic (or univariate) sensitivity analyses and probabilistic sensitivity analyses were pre-programmed using Microsoft® Visual Basic for Applications (VBA) with their inputs defined in the input parameters worksheets. The scenario analyses were performed manually.

1.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses were implemented to determine the extent of uncertainty around the ICER estimates. Random values were generated for specific parameter within a specified uncertainty distribution. This was performed for each parameter simultaneously and the resulting ICER was recorded, constituting one ‘simulation’. One thousand simulations were performed, providing a distribution (and uncertainty estimates) of ICERs.

For the probability of events occurring (such as the probability of adverse events), a beta distribution was applied to restrict values to between 0 and 1, in the same way that probabilities operate. For OS, PFS, progression to third-line therapy, and time to discontinuation Cholesky decomposition was used to account for the correlation between the regression parameters. A gamma distribution was fitted to costs only, as opposed to both resource use and costs – gamma distribution cannot fall below zero (but is otherwise unrestricted). The standard error of each parameter was the same as presented for the univariate sensitivity analyses. The distributions around specific parameters together with the deterministic estimates are presented in Table 24.

Although the probabilistic sensitivity analyses is conducted in a Bayesian framework, there are three principles and explicit judgements that are taken into account when a distribution is selected:

- The nature of the parameter itself
- The way the parameter was estimated
- Decision context.

Application of these general principles means that there will be only a very limited choice of appropriate distributional forms for the input parameters. Where a probability is estimated from a proportion, the beta distribution is the natural choice. If the probability parameter is estimated from a logistic regression / Cox regression, then the parameters of interest are the coefficients on the log-odds / log-hazard scale.[33] For cost input data, gamma or lognormal distributions are typically chosen because these functions usually well describe the distribution of costs in real life[34] and because these distributions do not allow negative costs.

Not all model parameters were subject to probabilistic sampling in the probabilistic sensitivity analyses. Variables that were derived from other parameters did not vary directly; their values varied because they were related to input parameters that were subject to probabilistic sampling. Structural model parameters (eg time horizon of the model) and the unit costs (including the cost of panobinostat) were not included in the probabilistic sensitivity analyses either. Finally, model settings that have been selected based on regulatory guidelines (eg dosing and discount rates) were held fixed as well.

Uncertainty around the model parameters are provided in Table 24.

1.8.2 Deterministic sensitivity analysis

In the current model structure, deterministic sensitivity analyses were generated using the upper and lower bounds of the 95% CI of each input parameter at a time. If the CI was not reported in the study from which a particular input parameter was derived, ± 2 times 20% of the mean (ie the deterministic) value of the input parameter was assumed as the upper and lower limit of the CI. Such practice is well accepted if uncertainty margins around an input parameter are unavailable. The upper and lower limits for specific parameters included are presented in Table 61 in the main submission dossier. Tornado plots were generated for costs and QALYs, separately, which ranked parameters from highest to lowest based on the magnitude of the result impact.

1.8.3 Scenario analysis

Scenario analyses were conducted around assumptions in the model and are presented in Table 35.

Table 35. Scenario analyses conducted with base values and scenario values

Parameter	Base Value	Scenario Value
Discount rate	3.5%	5%
Time Horizon	25 years	5 years
		10 years
Overall survival	Gompertz	Weibull
		Kaplan–Meier + best fitting model
Progression-free survival	Weibull	Gompertz
Time to discontinuation	Fitted curve	Kaplan–Meier estimates
Distribution of post-progression treatments	As presented in section 1.5.2	a) Equal to the full PANORAMA-1 population
		b) Equal to prior IMiD population of the PANORAMA-1 trial
Utility associated with LEN/DEX	Equal to BTZ/DEX	Equal to off-treatment interval
Methodology generating HRs for LEN/DEX versus PANO/BTZ/DEX	'Unadjusted Cox' (2 to 3 prior lines of treatment)	'Naïve' (ITT)
		'Unadjusted Cox' (ITT)
		'MAIC' (ITT)
		'Naïve' (2 to 3 prior lines of treatment)
Threshold analyses	-	Various HR of PFS and price scenarios

Notes: 'Kaplan–Meier + best fitting model' refers to a model that uses the Kaplan–Meier estimate until the maximum follow-up time and the best fitting model beyond the maximum follow-up time.

MAIC, matching adjusted indirect treatment comparison; Naïve, naïve, unadjusted indirect treatment comparison; common comparator, Common comparator based indirect treatment comparison; IMID, immunomodulatory drug

1.8.4 Summary of sensitivity analyses results – using 'Unadjusted Cox' method deriving HRs from data on subpopulation data of 2 to3 prior lines

Sensitivity analysis results are presented for the 'Unadjusted Cox' method deriving HRs from data on subpopulation data of 2 to 3 prior lines only applying the two price scenarios.

1.8.4.1 Results of the probabilistic sensitivity analysis

The results of the multivariate probabilistic sensitivity analysis of 1,000 simulations are presented in Figure 9 (scatter plot of total QALYs and costs),
Figure 10 (scatter plot of incremental QALYs and costs).

Probabilistic sensitivity analysis is run using the 'Unadjusted Cox' method and deriving HRs from subpopulation (2 to 3 prior lines) with both pricing scenario explored above

Figure 9. Scatter plot of simulated total QALYs versus total costs for PANO/BTZ/DEX and LEN/DEX (probabilistic sensitivity analysis), discounted analysis – using the 'Unadjusted Cox' method and deriving HRs from subpopulation (2 to 3 prior lines) – discounted

Base case: assuming £776 per 20 mg capsule

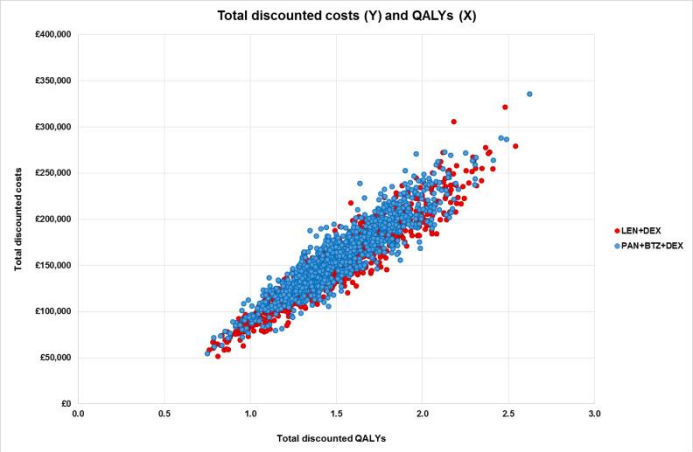
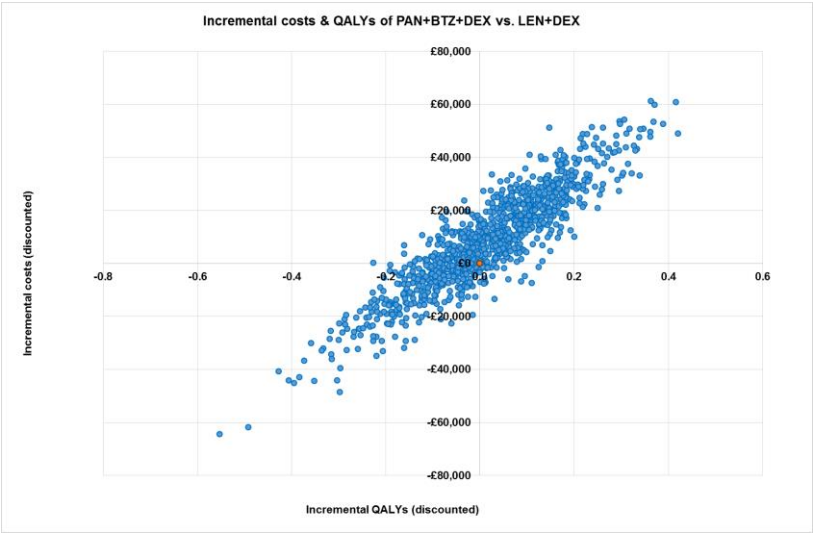


Figure 10. Simulated total incremental QALYs versus incremental costs of PANO/BTZ/DEX and LEN/DEX (probabilistic sensitivity analysis), discounted analysis – using the 'Unadjusted Cox' method and deriving HRs from subpopulation (2 to 3 prior lines) – discounted

Base case: assuming £776 per 20 mg capsule



With respect to the comparison between LEN/DEX and PANO/BTZ/DEX, the results of the probabilistic sensitivity analyses highlight that PANO/BTZ/DEX is associated with virtually the same QALY gains (mean incremental QALY is 0.044, 95% CI –0.32 to 0.34) and higher costs using the base case price scenario (mean incremental costs is £[redacted], 95% CI £[redacted] to £[redacted]).

Because both the simulated incremental QALY and cost outcomes tend to spread around zero, the lower the price of the PANO/BTZ/DEX combination treatment ends up, the higher the likelihood that starting third-line treatment with PANO/BTZ/DEX will result in a 'cost saving' treatment choice. In Figure 10, it is represented by the dots spreading around the y-axis (ie equal incremental QALYs) and below the x-axis (ie negative incremental costs).

The probabilistic sensitivity analysis resulted in the following 95% CIs around key model outcomes, which are presented in Table 36

Table 36. Values and 95% confidence intervals around key model outcomes

Base case: assuming £776 per 20 mg capsule

	Cost	**Mean incremental cost**	**QALYs**	**Incremental QALY**
PANO/BTZ/DEX	£[redacted] (£[redacted] to £[redacted])	£[redacted] (£[redacted] to £[redacted])	1.549 (1.045 to 2.142)	0.044 (–0.316 to 0.341)
LEN/DEX	£151,849 (£79,515 to £249,022)		1.505 (0.960 to 2.205)	

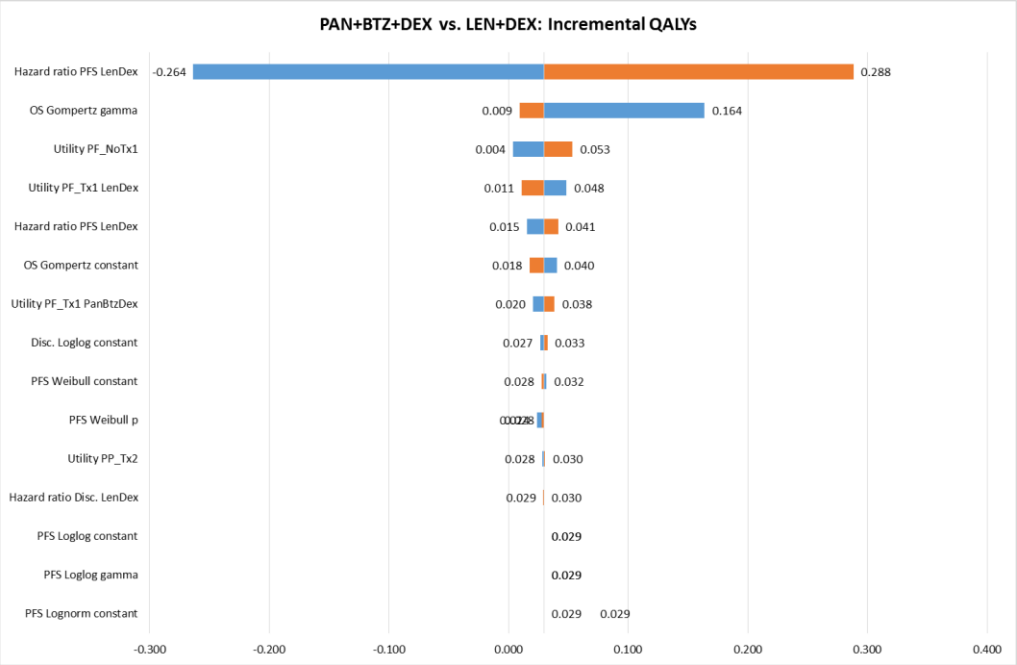
1.8.4.2 Results of the deterministic univariate sensitivity analysis

The tornado diagrams presenting the uncertainty in the incremental QALYs, incremental costs, and ICERs for the 15 most sensitive model parameters are depicted in Figure 11 to Figure 12.

In general, model outcomes (ie QALYs, costs) are sensitive to the HR estimating LEN/DEX relative efficacy (ie PFS and OS). However this can't be overcome given the circumstances (ie no clinical data available for LEN/DEX in the population with at least two prior therapies including an IMiD and bortezomib). Multiple modelling techniques have been tested in two datasets published on LEN/DEX with similar population data from PANORAMA-1 trial to increase the reliability of the current cost effectiveness calculations.

The model results seem to be even more sensitive to the cost of the PANO/BTZ/DEX triple combination treatment. It is worth noting that the relatively small QALY differences further significantly increase the sensitivity to this parameter given the method of ICER calculation.

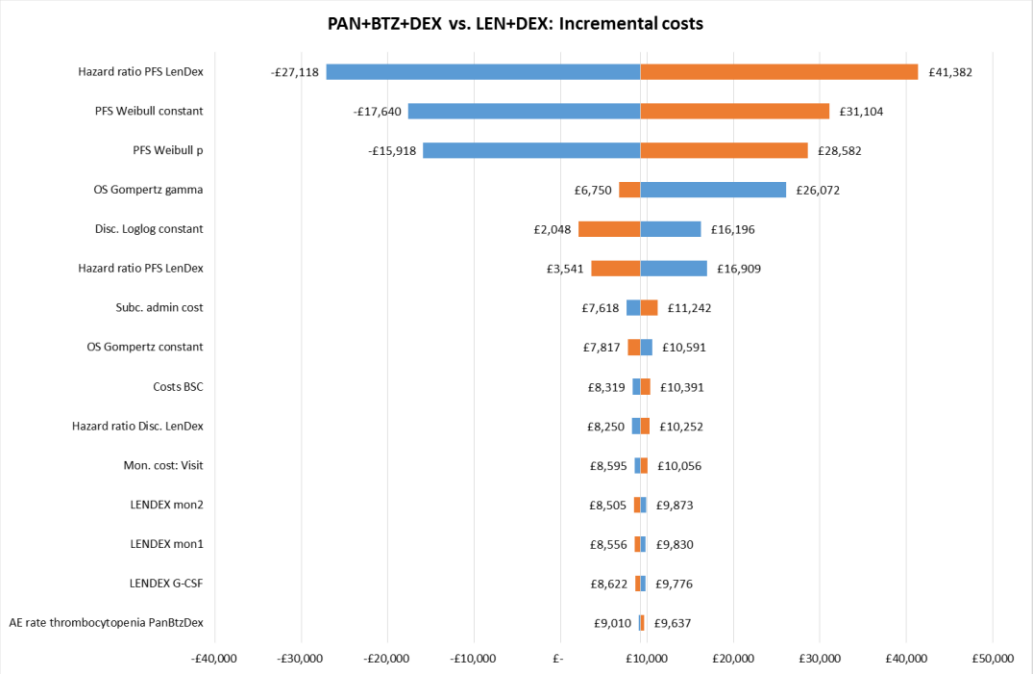
Figure 11. Tornado diagram of incremental QALYs for PANO/BTZ/DEX versus LEN/DEX using 'Unadjusted Cox' method deriving HRs from data on subpopulation data of 2 to 3 prior lines



BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; PANO, panobinostat; PFS, progression-free survival; QALY, quality-adjusted life years.

Figure 12. Tornado diagram of incremental costs for PANO/BTZ/DEX versus LEN/DEX assuming both pricing scenarios using 'Unadjusted Cox' method deriving HRs from data on subpopulation data of 2 to 3 prior lines

Base case: assuming £776 per 20 mg capsule



1.8.4.3 Results of the scenario analysis assuming both pricing scenarios using 'Unadjusted Cox' method deriving HRs from data on subpopulation data of 2 to 3 prior lines

Table 37. Results of the base case analysis

Base case: assuming £776 per 20 mg capsule

Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
£[redacted]	0.0518	0.102	£[redacted]	£[redacted]

ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

The results of the scenario analyses are presented through Table 38 to Table 43.

Discount rates

Table 38 indicates that using higher discount rate (5% instead of 3.5%) for costs and effects hardly changes the model outcomes relative to the base case results and hence there is no relevant difference in terms of the cost-effectiveness results.

Table 38. Results of scenario analysis: discount rate costs and effects 5%

Base case: assuming £776 per 20 mg capsule

Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
£10,031	0.0489	0.097	£204,938	£103,114

ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

Time horizon

Table 39 shows that a shorter time horizon the lower the incremental cost, while there is still slight incremental benefit associated to PANO/BTZ/DEX.

Table 39. Results of scenario analysis: Time horizon

Base case: assuming £776 per 20 mg capsule

Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
Time horizon: 5 years				
£9,138	0.0434	0.089	£210,554	£103,109
Time horizon: 10 years				
£[redacted]	0.0518	0.102	£[redacted]	£[redacted]

ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

Overall survival

Table 40 shows that the model results are robust to the three clinically plausible assumptions on the OS profile.

Table 40. Results of scenario analysis: overall survival

Base case: assuming £776 per 20 mg capsule

Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
Weibull				
£12,881	0.0735	0.136	£175,322	£94,990
Kaplan–Meier + best fitting				
£11,529	0.0626	0.119	£184,229	£97,220

ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

Progression-free survival

Similarly to the OS sensitivity analyses, Table 41 shows that the model results are robust to the two clinically plausible assumptions on the PFS profile.

Table 41. Results of scenario analysis: progression-free survival

Base case: assuming £776 per 20 mg capsule

Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
Gompertz				
£10,068	0.0514	0.102	£195,838	£98,977

ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

Time to discontinuation

Results presented in Table 42 indicate that using the Kaplan–Meier estimates to determine the risk of treatment discontinuation only slightly improves the incremental QALYs, LYs and incremental costs.

Table 42. Results of scenario analysis: Time to discontinuation

Base case: assuming £776 per 20 mg capsule

Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
Kaplan–Meier based				
£9,894	0.0518	0.102	£190,904	£97,261

ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

Distribution of fourth line treatments

Table 43 presents results when the post-progression treatment mix is based on post-progression treatments of the full PANORAMA-1 population and when it is based on post-progresssion treatments of the subpopulation with prior IMiD & bortezomib and ≥ 2 prior lines of treatment of the PANORAMA-1 trial. PANORAMA-1 based post progression treatment distributions improves the incremental QALYs, LYs and incremental costs.

Table 43. Results of scenario analysis: Distribution of fourth line treatments

Base case: assuming £776 per 20 mg capsule

Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
Full PANORAMA-1 population				
£7,731	0.0518	0.102	£149,279	£75,998
Prior IMiD population				
£7,266	0.0518	0.102	£140,312	£71,432

Notes:

Full PANORAMA 1 population treatment mix: 38.1% LEN/DEX, 6% BTZ/DOX, 21.6% BTZ/THAL/DEX, 29.8% BTZ/CYC/DEX, 4.5% POM/DEX.

Prior IMiD & bortezomib and ≥ 2 prior lines of treatment treatment mix: 34.6% LEN/DEX, 8.6% BTZ/DOX, 23.5% BTZ/THAL/DEX, 33.3% BTZ/CYC/DEX, 0% POM/DEX.

Utility associated with LEN/DEX equal to off-treatment

Results presented in Table 44 indicate that assuming LEN/DEX treatment is not associated with any disutility does not change the conclusions of the model. All the cost, the QALY and the LY increments still remain close to zero.

Table 44. Results of scenario analysis: no utility decrement on LEN/DEX

Base case: assuming £776 per 20 mg capsule

Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
£10,189	0.0483	0.102	£210,747	£100,166

DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LY, life year; QALY, quality-adjusted life year.

Various methodologies applied to generate PFS and OS HRs for LEN/DEX versus PANO/BTZ/DEX

Results presented in Table 45 reiterate the model's sensitivity to the PFS and OS HRs of LEN/DEX versus PANO/BTZ/DEX.

Table 45. Results of scenario analysis: various methodologies applied

Base case: assuming £776 per 20 mg capsule

Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
'Unadjusted Cox' (ITT)				
£5,336	–0.0230	–0.004	dominated	dominated
'MAIC' (ITT)				
£9,255	0.0295	0.071	£313,846	£129,496
'Naïve' (2 to 3 prior lines of treatment)				
–£5,381	–0.0465	–0.061	£115,752	£88,890

ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LY, life year; MAIC, matching adjusted indirect treatment comparison; QALY, quality-adjusted life year.

Threshold analyses

Table 46 presents results when the various HR of PFS for LEN/DEX versus PANO/BTZ/DEX is used (assumed capsule price is set to base case). The analyses revealed that the higher the HR the higher the cost saving is.

Table 46. Results of scenario analysis: various HR of PFS input data for LEN/DEX – assumed mg price is set to base case

Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
HR = 0.8				
£18,572	0.036	0.358	£515,863	£51,853
HR = 0.9				
£14,726	0.043	0.358	£342,702	£41,115
HR = 1				
£11,717	0.049	0.358	£240,423	£32,715
HR = 1.1				
£9,303	0.054	0.358	£173,569	£25,974
HR = 1.2				
£7,323	0.058	0.358	£126,774	£20,444

DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LY, life year; PFS, progression-free survival; QALY, quality-adjusted life year.

1.9 Validation

1.9.1 Validation of de novo cost-effectiveness analysis

Expert validation

Excel formulas, model logic and input data were verified for accuracy as part of quality-control procedures by an experienced modeller not involved in the model development. Notably, excel formulas were checked to ensure they reflect the logic of the model. In addition, the model was varied within extreme value beyond what would be considered “reasonable” to ascertain whether the change in the simulated costs and utilities was consistent with a priori expectation. Model predictions were also compared to observed data when possible.

Limitations of the model

Lenalidomide among the prior 'IMiD' category

The current analyses use data from the PANORAMA-1 trial from patients who had received at least two prior lines of treatment including a prior IMiD and bortezomib based regimen (n = 73). Although this population matches the patient population of the UK clinical practice in the third (or later) line treatment setting; for the purpose of the LEN/DEX compariosn, assuming no re-challenge with LEN/DEX), patients who had received at least two prior lines of treatment including thalidomide only and bortezomib based regimen should be used (n = 63).

On the one hand using such population would further decrease the population size based on which model input data is derived and hence would further increase the uncertainty around the cost-effectiveness analysis estimates.

On the other, in this further restricted population, the median PFS is 12.5 months (95% CI: 8.1 to 14.2), the median OS is [redacted], 95% CI: [redacted] to [redacted]), median treatment duration is 4.8 months (95% CI: 3.4 to 7.8). Comparing these estimates with the estimates of the population used for the current analysis as well as the estimates of the model, it can be concluded that the populations are very similar (see Table 28 in section 1.7.2).

Limitations related to published data on LEN/DEX

As described in section 1.2.1 no treatment comparison could be performed based on patients who received at least two prior lines of treatment inlcuding bortezomib and an IMiD. Unfortunately, this limitation cannot be overcome given the circumstances (ie no clinical data available for LEN/DEX in this population). However, multiple modelling techniques have been tested in two datasets published on LEN/DEX with similar population data from PANORAMA-1 trial to increase the reliability of the current cost effectiveness calculations to provide the best possible comparison between the two regimens.

Post-progression treatments seem to have not been reported for LEN/DEX. Therefore the potential impact of the differences in the post-progression treatments (panobinostat versus lenalidomide) on survival could not be assessed.

There was a mismatch between the efficacy data (PFS, OS, treatment duration – from Dimopoulos et al. 2009, Stadtmauer et al. 2009, combined MM-009/010 trial data) used for the indirect treatment comparisons and the data used for the treatment costs of LEN/DEX (TA171 NICE Guidance based on the European MM-010 trial only). Given the lack of LEN/DEX treatment cost data based on the combined MM-009/010 trials, it is unclear how such difference affects the cost-effectiveness analysis

results. Also, four-weekly cost of LEN/DEX were rescaled to 3-weekly cost, which may also introduce some bias.

Limitations related to other published data sources

There may be some double counting of terminal care costs as it is not clear from the study of Gooding et al whether end of life care costs were included in their study or not. However, because the difference between the OS profiles of the PANO/BTZ/DEX and LEN/DEX is minor, the inclusion or exclusion of terminal care costs has a negligible impact on the results.

1.10 Interpretation and conclusions of economic evidence

2 Assessment of factors relevant to the NHS and other parties

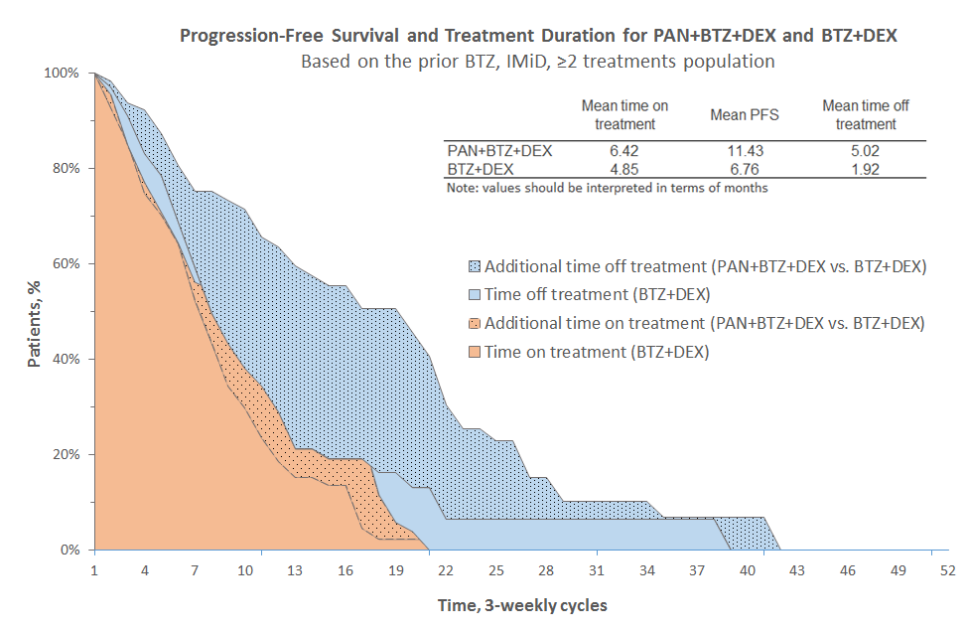
3 References

1. National Institute for Health and Care Excellence. Technology Appraisal 129: Bortezomib monotherapy for relapsed multiple myeloma. October 2007. Available at: www.nice.org.uk/TA129. (Accessed 4 October 2013).
2. Green C, Bryant J, Takeda A *et al.* Bortezomib for the treatment of multiple myeloma patients. *Health Technol Assess* 2009;13 (Suppl 1):29–33.
3. Hornberger J, Rickert J, Dhawan R *et al.* The cost-effectiveness of bortezomib in relapsed/refractory multiple myeloma: Swedish perspective. *Eur J Haematol* 2010;85 484–91.
4. Moller J, Nicklasson L, Murthy A. Cost-effectiveness of novel relapsed-refractory multiple myeloma therapies in Norway: lenalidomide plus dexamethasone vs bortezomib. *J Med Econ* 2011;14 690–7.
5. National Institute for Health and Care Excellence. Technology Appraisal 171: Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. June 2009. Available at: http://www.nice.org.uk/TA171. (Accessed 4 October 2013).
6. Brown RE, Stern S, Dhanasiri S, Schey S. Lenalidomide for multiple myeloma: cost-effectiveness in patients with one prior therapy in England and Wales. *Eur J Health Econ* 2013;14 507–14.
7. Fragoulakis V, Kastritis E, Psaltopoulou T, Maniadakis N. Economic evaluation of therapies for patients suffering from relapsed-refractory multiple myeloma in Greece. *Cancer Manag Res* 2013;5 37–48.
8. Celgene. NICE Single Technology Appraisal (STA) - Pomalidomide for relapsed and refractory multiple myeloma. June 2014.
9. Stadtmauer EA, Weber DM, Niesvizky R *et al.* Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma. *Eur J Haematol* 2009;82:426–32.
10. San-Miguel JF, Hungria VT, Yoon SS *et al.* Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. *Lancet Oncol* 2014;15:1195–206.
11. Moreau P, San Miguel J, Ludwig H *et al.* Multiple myeloma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24 (Suppl 6):133–7.
12. Hoyle M, Rogers G, Moxham T, Liu Z, Stein K. Cost-effectiveness of dasatinib and nilotinib for imatinib-resistant or -intolerant chronic phase chronic myeloid leukemia. *Value Health* 2011;14:1057–67.
13. Gooding S, Lau I-J, Sheikh M *et al.* Double refractory myeloma: analysis of clinical outcomes and medical-resource utilisation in a single centre *Blood* 2013;122:Abstract 1727.
14. National Institute for Health and Clinical Excellence. Technology Appraisal 171: Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. June 2009. Available from: http://www.nice.org.uk/TA171. (Accessed 4 October 2013).
15. National Institute for Health and Care Excellence. Technology Appraisal 228: Bortezomib and thalidomide for the first-line treatment of multiple myeloma. July 2011. Available from: https://www.nice.org.uk/guidance/ta228 (Accessed 5 June 2014).
16. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Available at: http://www.nice.org.uk/article/pmg9/chapter/Foreword (Accessed 12 March 2015).
17. Dimopoulos MA, Chen C, Spencer A *et al.* Long-term follow-up on overall survival from the MM–009 and MM–010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. *Leukemia* 2009;23 2147–52.
18. San Miguel J, Weisel K, Moreau P *et al.* Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *The lancet oncology* 2013;14:1055–66.
19. Kvam AK, Fayers PM, Wisloff F. Responsiveness and minimal important score differences in quality-of-life questionnaires: a comparison of the EORTC QLQ-C30 cancer-specific questionnaire to the generic utility questionnaires EQ-5D and 15D in patients with multiple myeloma. *Eur J Haematol* 2011;87:330–7.

20. Osborne TR, Ramsenthaler C, Siegert RJ *et al.* What issues matter most to people with multiple myeloma and how well are we measuring them? A systematic review of quality of life tools. *Eur J Haematol* 2012;89:437–57.
21. Gulbrandsen N, Hjermstad MJ, Wisloff F. Interpretation of quality of life scores in multiple myeloma by comparison with a reference population and assessment of the clinical importance of score differences. *Eur J Haematol* 2004;72:172–80.
22. Johnsen AT, Tholstrup D, Petersen MA, Pedersen L, Groenvold M. Health related quality of life in a nationally representative sample of haematological patients. *Eur J Haematol* 2009;83:139–48.
23. Aaronson NK, Ahmedzai S, Bergman B *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365–76.
24. Acaster S, Gaugris S, Velikova G, Yong K, Lloyd AJ. Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: a UK cross-sectional survey. *Support Care Cancer* 2013;21:599–607.
25. van Agthoven M, Segeren CM, Buijt I *et al.* A cost-utility analysis comparing intensive chemotherapy alone to intensive chemotherapy followed by myeloablative chemotherapy with autologous stem-cell rescue in newly diagnosed patients with stage II/III multiple myeloma; a prospective randomised phase III study. *Eur J Cancer* 2004;40:1159–69.
26. Petrucci MT, Calabrese E, Levi A *et al.* Costs and quality of life of multiple myeloma (MM) in Italy: the CO.MI.M study. *Value Health* 2009;12:A265.
27. Dubois D, Dhawan R, van de Velde H *et al.* Descriptive and prognostic value of patient-reported outcomes: the bortezomib experience in relapsed and refractory multiple myeloma. *J Clin Oncol* 2006;24 976–82.
28. National Audit Office. End of life care. 2008. Available from: http://www.nao.org.uk/wp-content/uploads/2008/11/07081043.pdf (Accessed: 14 January 2014).
29. Mosteller RD. Mosteller body-surface area calculator. Available from: http://www.patient.co.uk/doctor/body-surface-area-calculator-mosteller (Accessed March 2015).
30. Department of Health. National schedule of reference costs 2012–2013. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013 (Accessed March 2015).
31. Pomalidomide (Imnovid). Summary of product characteristics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002682/WC500147717.pdf (Accessed March 2015).
32. Haematological Malignancy Research Network. Clinical management and outcome of myeloma. Version 3.0.
33. Claxton K. Exploring uncertainty in cost-effectiveness analysis. *Pharmacoeconomics* 2008;26:781–98.
34. Drummond M, Barbieri M, Cook J *et al.* Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. *Value Health* 2009;12:409–18.

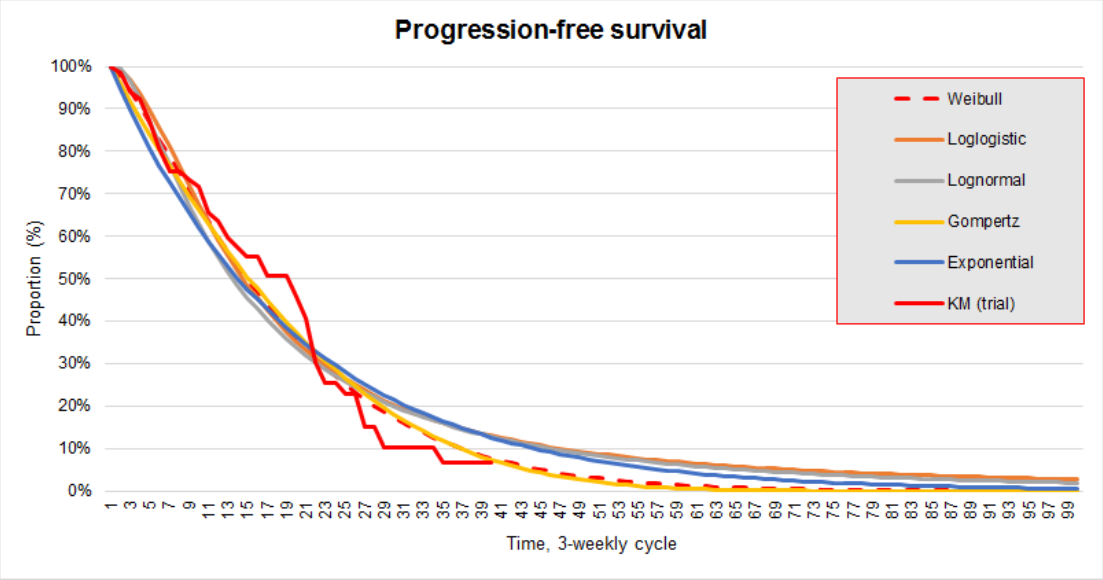
4 Progression-free survival by investigator assessment and treatment duration

Figure 13 Progression-free survival by investigator assessment and treatment duration, prior IMiD+ bortezomib population



5 Observed and predicted progression-free survival

Figure 14 Observed and predicted progression-free survival, PANO/BTZ/DEX



6 Observed and predicted overall survival

Figure 15 Observed and predicted overall survival, PANO/BTZ/DEX

7 Visit evaluation schedule (based on the PANORAMA-1 clinical trial protocol)

	Screening [1]	Treatment phase 1									Treatment phase 2				Follow-up phase				
		Cycle 1 [2] (day 1 to 21)					Cycle 2 to cycle 8 [2] (day 1 to 21)				Cycle 9 - 12 [2,3] (day 1 to 42)				End of Treatment	28 day Follow-up [28]	Follow-up [28]	Study Evaluation Completion [29]	Survival [30]
Visit no.	1	2	3	4	5	6	7 11 15 19 23 27 31	8 12 16 20 24 28 32	9 13 17 21 25 29 33	10 14 18 22 26 30 34	35 39 43 47	36 40 44 48	37 41 45 49	38 42 46 50	777	501	502, 503	778	701
Day of cycle	- 21 to -1	1	4	5	8	11	1	4	8	11	1	8	22	29	---	---	---	---	---
Demography/ informed consent	X																		
Inclusion/exclusion criteria	X																		
Medical history/ current medical conditions	X																		
Diagnosis & history of multiple myeloma	X																		
Prior antineoplastic therapy	X																		
Vital signs	X	X[1]		X			X				X				X				
Height	X																		
Weight / BSA	X	X[1]					X				X				X				
Physical examination	X	X[1]					X				X				X				
ECOG performance status	X	X[1]					X				X				X				
12-lead ECG [4, 5]	X	X[1]		X			X												

	Screening [1]	Treatment phase 1									Treatment phase 2				Follow-up phase				
		Cycle 1 [2] (day 1 to 21)					Cycle 2 to cycle 8 [2] (day 1 to 21)				Cycle 9 - 12 [2,3] (day 1 to 42)				End of Treatment	28 day Follow-up [28]	Follow-up [28]	Study Evaluation Completion [29]	Survival [30]
Visit no.	1	2	3	4	5	6	7 11 15 19 23 27 31	8 12 16 20 24 28 32	9 13 17 21 25 29 33	10 14 18 22 26 30 34	35 39 43 47	36 40 44 48	37 41 45 49	38 42 46 50	777	501	502, 503	778	701
Day of cycle	- 21 to -1	1	4	5	8	11	1	4	8	11	1	8	22	29	---	---	---	---	---
LVEF (MUGA or ECHO)	X	X[1]																	
Hematology [5, 8]	X[7]	X[1]	X		X	X	X	X	X	X	X	X	X	X	X				
Coagulation [10]	X[7]																		
Biochemistry [11]	X[7]	X[1]				X	X[9]			X	X[9]		X		X		X[33]		
Urinalysis [12]	X																		
Calculated Creatinine Clearance	X[7]						X				X				X				
Pregnancy test	X[13]														X[14]				
PRO/QoL questionnaires (QLQ-C30, MY20, FACT GOG/NTx) [15,15a]	X	X					X				X							X	
Patient/Investigator Global Change [15,15b]							X											X	
Patient/Investigator Global Severity [15, 15c]	X						X												
Thyroid function [16]	X						X								X				
Disease status																			

	Screening [1]	Treatment phase 1									Treatment phase 2				Follow-up phase				
		Cycle 1 [2] (day 1 to 21)					Cycle 2 to cycle 8 [2] (day 1 to 21)				Cycle 9 - 12 [2,3] (day 1 to 42)				End of Treatment	28 day Follow-up [28]	Follow-up [28]	Study Evaluation Completion [29]	Survival [30]
Visit no.	1	2	3	4	5	6	7 11 15 19 23 27 31	8 12 16 20 24 28 32	9 13 17 21 25 29 33	10 14 18 22 26 30 34	35 39 43 47	36 40 44 48	37 41 45 49	38 42 46 50	777	501	502, 503	778	701
Day of cycle	- 21 to -1	1	4	5	8	11	1	4	8	11	1	8	22	29	---	---	---	---	---
Serum M-protein (S-PEP) [17]	X	X[18]					X				X		X		X[19]		X[19]		
Urine M-protein (U-PEP) [17]	X	X[18]					X				X		X		X[19]		X[19]		
Serum Free light chain (FLC) [22]							X				X								
Serum Immunofixation (sIF) [17]	X						X				X		X		X		X		
Urine Immunofixation (uIF) [17]	X						X				X		X		X		X		
Skeletal survey (Bone X-ray) [20]	X																		
Evaluation of soft-tissue plasmacytomas [21]	X						X				X		X		X		X		
Bone Marrow for plasma cell count and for flow cytometry [23, 24]	X																		
Panobinostat/Placebo Blood PK samples		X[31]			X[31]														

	Screening [1]	Treatment phase 1									Treatment phase 2				Follow-up phase				
		Cycle 1 [2] (day 1 to 21)					Cycle 2 to cycle 8 [2] (day 1 to 21)				Cycle 9 - 12 [2,3] (day 1 to 42)				End of Treatment	28 day Follow-up [28]	Follow-up [28]	Study Evaluation Completion [29]	Survival [30]
Visit no.	1	2	3	4	5	6	7 11 15 19 23 27 31	8 12 16 20 24 28 32	9 13 17 21 25 29 33	10 14 18 22 26 30 34	35 39 43 47	36 40 44 48	37 41 45 49	38 42 46 50	777	501	502, 503	778	701
Day of cycle	- 21 to -1	1	4	5	8	11	1	4	8	11	1	8	22	29	---	---	---	---	---
Bortezomib Blood PK samples					X[32]														
Bortezomib bolus intravenous injection		X	X		X	X	X	X	X	X	X	X	X	X					
Panobinostat / Placebo		Days 1-3 -5 + 8-10-12 (3 times weekly, 2 weeks on & 1 week off, 21 days cycle)									Days 1-3-5, 8-10-12 & 22-24-26, 29-31-33 (42 days cycle)								
Dexamethasone		Days 1-2-4-5 + 8-9-11-12									Days 1-2-8-9 + 22-23-29-30								
Adverse Events [25]	X	Continuous																	
Prior/Concomitant medications [26]	X	Continuous																	
Anti-neoplastic medications since discontinuation of study treatment [27]															X	X	X	X	X

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Single Technology Appraisal (STA)

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy [ID663]

Dear [redacted]

The Evidence Review Group, PenTAG, and the technical team at NICE have now had an opportunity to take a look at the submission received on Wednesday 20 May by Novartis. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm, Thursday 25 June 2015**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be uploaded to NICE Docs/Appraisals via this link: <<Insert NICE DOCS LINK>>.

If you have any further queries on the technical issues raised in this letter then please contact Caroline Hall, Technical Lead (caroline.hall@nice.org.uk). Any procedural questions should be addressed to Lori Farrar, Project Manager (lori.farrar@nice.org.uk) in the first instance.

Yours sincerely

Dr Frances Sutcliffe
Associate Director – Appraisals

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Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on clinical-effectiveness data

A1. **Priority Question**: Page 21 – in the third paragraph the median overall survival is stated as being extended by 11.0 months (from 195 months to 305 months). Please could you provide mean overall for the 2 subgroups on which the cost-effectiveness is based?

A2. **Priority Question**: Page 48 (Figure 7) of the submission stated that 87 studies were excluded by title or abstract. Should this number be 386?

A3. **Priority Question**: The date, month and year of each search is provided in the submission. Please could you also provide the data parameters of the databases you searched on these days (for example Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present)?

A4. **Priority Question**: Please could you confirm which database host was used to search EMBASE?

A5. **Priority Question**: The submission states that the Cochrane Library was searched. Please confirm whether this included the CENTRAL and the HTA database? Please also provide the data parameters of each library searched (for example Cochrane Database of Systematic Reviews: Issue 6 of 12, June 2015).

A6. **Priority Question**: Page 137 – the submission states that further trial data is anticipated to be available in May/June 2015. Is these data available?

A7. **Priority Question:** The searches used in the submission were carried out over 6 months ago. Please carry out these searches again providing the results along with the data parameters of the databases searched and any new studies clearly marked.

A8. **Priority Question**: Please provide information on how the study design or publication type limits were applied. For example, the EMBASE search strategy on page 4 (section 8.2, line 27), please provide details of how you limited the randomised controlled trials and the phases of the clinical trials.

A9. Please can you confirm that the omission of the following search terms for Panobinostat have not prohibited the identification of studies: Farydak or Faridak.

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A10. Please confirm why 2003 was chosen as the start date of the literature searches.

A11. **Priority Question**: Page 76 (table 12) of the submission provides median survival figures of 38.24 months and 35.38 months in PANO/BTZ/DEX and BTZ/DEX groups, respectively based on the data cut-off of September 2013. However, on page 20 of the submission these data are presented but the submission states that the data cut-off is 18th August 2014. On page 82 cut-off data relating to 18th August 2014 is provided but the figures are different (33.64 and 30.39 months are reported as the corresponding figures for OS at 10 September 2013) and these data are also provided on page 130 but relating to the second interim overall survival analysis. Please clarify what the median overall survival figures were as of September 2013 and August 2014 and any subsequent time points alongside estimates of mean overall survival in PANO/BTZ/DEX and BTZ/DEX groups, respectively.

A12. **Priority Question**: Page 24 – the summary of the cost-effectiveness reports total survival for PANO/BTZ/DEX and BTZ/DEX groups of 3.57 years and 2.797 years, respectively, which equates to 42.84 and 33.56 months in the two groups. with respect to this data please clarify the following:

a. which approach has been used to estimate survival for the purposes of the cost-effectiveness calculations?

b. why the mean survival used in the cost-effectiveness analysis for PANO/BTZ/DEX patients is greater than the reported median overall survival while the survival of BTZ/DEX patients used in the cost-effectiveness analysis is lower than the median reported overall survival?

A13. Page 75 (table 17) of the submission details that the median time to response for patients achieving CR/nCR according to investigator assessment was the same as the lower bound of 95%[0.76 (0.76-0.95)]. Please could you confirm this is correct and explain why this might be the case? The same applies to the data for patients achieving PR according to investigator assessment box [1.41 (1.41-1.51)].

A14. **Priority Question**: Pages 75 to 78 (section 4.7.4) of the submission states that the mean time a patient remained treatment-free up to progression was 7.49 months in the PANO/BTZ/DEX group compared with 3.86 months in the BTZ/DEX group. For the mean survival data used in the cost-effective analysis please provide the mean time spent in the pre-progression state, no treatment state and the post-progression state for PANO/BTZ/DEX and BTZ/DEX groups, respectively.

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A15. **Priority Question**: Please provide the Kaplan-Meier curve for overall survival for the whole sample in the PANORAMA-1 study (the equivalent of Figure 24, p. 89 for all patients in the study), together with the underlying data.

A16. **Priority Question**: Page 104 (table 25) – please clarify how the overall survival comparisons between PANO/BTZ/DEX and LEN/DEX (for example 38.24 months or 3.2 years for PANO/BTZ/DEX based on the full population), relate to the figures for life years gained reported on page 25 (table 3c) (for example 2.288 years for PANO/BTZ/DEX based on full trial populations)?

A17. **Priority Question**: Page 105 (table 25a and b) – the progression-free and overall survival for the full population and the subpopulation with 2 to 3 prior lines of treatment, under the method of naïve comparison between PANO/BTZ/DEX and LEN/DEX, are reported. Please clarify the corresponding figures for the other methods of comparison.

Section B: Clarification on cost-effectiveness data

B1. **Priority Question**: Please clarify why the Personal Social Services perspective has not been taken into account.

B2. **Priority Question**: Please clarify how the searches for the cost-effectiveness data were carried out and explain why conference material was removed at the database search and then hand-searched. Please also confirm whether all published and unpublished trial data has been included.

B3. **Priority Question**: The date limits of the study searches for the cost and economic data are inconsistent. On page 17 (section 8.11 of appendix) the searches were limited to 2003 whereas on pages 18 to 20 is limited to 2006 and on page 20 to 23, for the MEDLINE search the data is limited to 2003 until current on line 66 but on line 67 the dates are limited to 2006 until current time. Please indicate which is correct and carry out one of the following:

a. If the cost-effectiveness searches were carried out from 2006 onwards rather than 2003, please consider any conflict this has with the presentation of studies for this submission and/or any impact on the broader submission synthesis or impact on the model

b. If the searches were carried out from 2003 onwards please carry out your cost-effectiveness searches as presented on pages 18-23 (that is without the additional intervention terms you use in the 2013-2014 search) for the dates 2003-2006. This search will need to be screened to the same inclusion/exclusion criteria. Please highlight any new studies identified.

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B4. Please clarify why the NHS EEDs database was only searched for studies published or indexed in 2014 when the database was updated until January 2015.

B5. **Priority Question**: Page 148 (table 40) in the submission details that exponential functions have been used to model risk of progression and risk of death in those receiving BTZ/DEX who discontinue treatment without disease progression and those who receive LEN/DEX/last line of treatment. Please clarify why the same approach was not used for those receiving PANO/BTZ/DEX, those receiving BTZ/DEX in cycles 1-4 and BTZ/DEX responders in cycles 5-8?

B6. **Priority Question**: Page 151 (section 5.3.1) in the submission states:

'Transition probabilities for the risk of death in patients receiving LEN/DEX and the subsequent LLoT were derived from patient-level post-progression OS data from PANORAMA-1 for patients who received LEN/DEX as subsequent antineoplastic treatment after PANO/BTZ/DEX or BTZ/DEX. Transition probabilities for LEN/DEX and LLoT were assumed to be the same for both treatment groups (ie patients initially receiving PANO/BTZ/DEX or BTZ/DEX)'.

It is then stated that:

'The risk of progression on LEN/DEX and the risk of post-progression death was assumed to be the same for both treatment groups (ie after PANO/BTZ/DEX and after BTZ/DEX) because no statistical difference between the treatment arms was established for post-progression death (see Appendix 16 for details). … Data for progression in patients receiving subsequent antineoplastic treatments after PANO/BTZ/DEX or BTZ/DEX was not collected in the PANORAMA-1 trial. Instead, the risk of progression or death on LEN/DEX treatment (or leaving LEN/DEX health state) was estimated using published data for PFS from the pooled MM-009 and MM-010 studies'.

Please clarify at what points in the clinical pathway data other than that from PANORAMA-1 is used to model progression and/or death and the assumptions being made about progression and/or death in the PANO/BTZ/DEX and BTZ/DEX groups, respectively.

B7. **Priority Question**: Page 25 of main submission and pages 56 and 71 of appendix 17 - Please provide the cost-effectiveness ratio of PANO/BTZ/DEX compared with BTZ/DEX for the 2 subgroups.

B8. **Priority Question**: Page 172 in the submission states that the health–related quality of life (HRQL) data notes that 'The cycle-specific mapped utility values

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were lower for PANO/BTZ/DEX than for BTZ/DEX at all time points, as expected from the differences in safety profile between the two treatments'. Please explain why the utility associated with the 'pre-progression, no-treatment' health state was mapped from the last HRQL assessment while still on treatment using **pooled data from both treatment groups**. If possible please separately report results using HRQL data while still on treatment for PANO/BTZ/DEX and BTZ/DEX groups.

B9. **Priority Question**: There are slight differences between cost reported in Table 58, section 5.5.3 (page 191) and section 5.5.2 (page 187), to which table 58 refers (for example, an average cost of £5,366 in the first treatment phase for PANO/BTZ/DEX in table 58 compared with £5,375 in section 5.5.2). Please confirm the unit costs used in the economic model.

B10. **Priority Question**: Page 173 (paragraph 4) in the submission states 'No HRQL data from PANORAMA 1 were available for the post-progression health states. Instead, utility values published by van Agthoven et al were used…'. Please clarify whether the formal search was undertaken to identify studies reporting utility values and how the paper by van Agthoven et al. was selected?

B11. **Priority Question**: Page 193 (section 5.5.4, last paragraph) states that no indirect costs were included in management of adverse effects 'Only direct costs were taken into account and no differentiation was made between inpatient and outpatient management costs'. Please explain the rationale for not including indirect costs.

B12. Page 194 (section 5.5.5) - the submission states that '…it was assumed that 20% of the patients that die actually receive terminal care…'. Please clarify the rationale for using 20%.

B13. Please clarify if and how the results of the PANORAMA-2 trial are incorporated into the model.

B14. **Priority Question:** Appendix 17, page 59 (table 27) of the submission, the life years gained and QALY results for PANO/BTZ/DEX under MAIC (for the comparison of PANO/BTZ/DEX and LEN/DEX) derive hazard ratios from full trial populations and Unadjusted Cox deriving HRs from the subpopulation (2 to 3 prior lines) appear to be identical. Please clarify the differences in the data sets used to model survival under MAIC full population and Unadjusted Cox subpopulation approaches.

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Section C: Textual clarifications and additional points

C1. **Priority Question**: please clarify the reason for not conducting a search for adverse events.

C2. **Priority Question**: Please clarify whether the terms 'relapsed and refractory multiple myeloma' and 'multiple myeloma in people who have received at least one prior therapy' are being used interchangeably.

C3. **Priority Question**: Please clarify whether the terms 'subpopulation with prior ImiD and bortezomib and >= 2 prior lines of treatment' and 'subpopulations with 2 to 3 prior lines of treatment' are being used interchangeably.

C4. **Priority Question**: Please clarify the reasons for focussing the subgroup analysis on a comparison of PANO/BTZ.DEX relative to LEN/DEX in patients treated with 2 to 3 prior lines of therapy, rather than a comparison of PANO/BTZ/DEX with BTZ/DEX in the same subgroup.

C5. Page 59 of the submission states that a planned second interim analysis was not performed. Please clarify why this was not performed and if it is to be performed, when it is planned.

C6. Please confirm whether events for final progression-free survival and overall survival have been observed and if so please provide the data.

C7. The submission states that CHMP opinion is due in May/June 2015. Please could you confirm whether this opinion has been received and if so please provide the wording.

C8. Please consider lifting the confidentiality marking, for example the 'commercial in confidence' marking of the overall survival Kaplan-Meier data and post-progression curves in your company submission, to be in line with NICE processes. The NICE team will send you a more detailed request of items requiring consideration in due course.

Single Technology Appraisal (STA)

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy [ID663]

Manufacturer's response to the clarification questions

Section A: Clarification on clinical-effectiveness data

A1. **Priority Question**: Page 21 – in the third paragraph the median overall survival is stated as being extended by [redacted] months (from [redacted] months to [redacted] months). Please could you provide mean overall for the 2 subgroups on which the cost-effectiveness is based?

***Response**: Both cost effectiveness models, i.e. the model developed for the broad label against BTZ/DEX and for the restricted label against Len/DEX, use patient level data, hence mean OS was not used as input data in either of them.*

Mean OS data can be retrieved from both models as output data calculated by the area under the modelled OS curves.

- *Mean OS (model output) is 42.84 months in the model assuming broad label (Table 63 in the submission)*
- *Mean OS (model output) is 27.46 months in the model assuming restricted label (table 27 in Appendix 17)*

A2. **Priority Question**: Page 48 (Figure 7) of the submission stated that 87 studies were excluded by title or abstract. Should this number be 386?

***Response**: Yes, the correct number should indeed be 386.*

A3. **Priority Question**: The date, month and year of each search is provided in the submission. Please could you also provide the data parameters of the databases you searched on these days (for example Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present)?

***Response:** The Ovid database for MEDLINE® and Embase was from 1974-present; the Cochrane Library databases searched were from 1956 – present.*

A4. **Priority Question**: Please could you confirm which database host was used to search EMBASE?

***Response:** All electronic searches were performed through Ovid.*

A5. **Priority Question**: The submission states that the Cochrane Library was searched. Please confirm whether this included the CENTRAL and the HTA database? Please also provide the data parameters of each library searched (for example Cochrane Database of Systematic Reviews: Issue 6 of 12, June 2015).

Response: *All Cochrane libraries were searched, including CENTRAL and HTA. The searches were performed in June 2013, May 2014 and December 2014.*

A6. **Priority Question**: Page 137 – the submission states that further trial data is anticipated to be available in May/June 2015. Is these data available?

Response: *Subgroup specific data has been published at EHA 2015 Congress. Confidentiality marking on this data has been lifted and resubmitted to NICE on 23rd June. Despite our earlier expectations, the final overall survival data is planned to be published in December at the 57th ASH Congress, should the required number of events happen in time for data submission.*
The anticipated label is expected to become published on the EMA website on 26th June together with the EPAR.

A7. **Priority Question:** The searches used in the submission were carried out over 6 months ago. Please carry out these searches again providing the results along with the data parameters of the databases searched and any new studies clearly marked.

Response: *The last systematic review update was carried out on 9th December with the results shared in the submission on the 20th May within the 6 months limit in line with the respective Guidance.*

A8. **Priority Question**: Please provide information on how the study design or publication type limits were applied. For example, the EMBASE search strategy on page 4 (section 8.2, line 27), please provide details of how you limited the randomised controlled trials and the phases of the clinical trials.

Response: *Searches were electronically limited, using the limit functionality in Ovid, to publications that were categorized as one of the following: Randomized controlled trial, Phase 2 trial, Phase 3 trial or Phase 4 trial.*

A9. Please can you confirm that the omission of the following search terms for Panobinostat have not prohibited the identification of studies: Farydak or Faridak.

Response: *The omission of the brand term did not prohibit studies being identified as the terms panobinostat, LBH589 and LBH-589 were used. This was consistent with the original search.*

A10. Please confirm why 2003 was chosen as the start date of the literature searches.

Response: *the initial systematic review, performed in 2013, aimed to assess the published literature for a 10-year time period. This was considered to be the relevant time period given that the pivotal trials for the agents of particular interest, namely bortezomib, lenalidomide and pomalidomide were published after 2003.*

A11. **Priority Question**: Page 76 (table 12) of the submission provides median survival figures of 38.24 months and 35.38 months in PANO/BTZ/DEX and BTZ/DEX groups, respectively based on the data cut-off of September 2013. However, on page 20 of the submission these data are presented but the submission states that the data cut-off is 18th August 2014. On page 82 cut-off data relating to 18th August 2014 is provided but the figures are different (33.64 and 30.39 months are reported as the corresponding figures for OS at 10 September 2013) and these data are also provided on page 130 but relating to the second interim overall survival analysis. Please clarify what the median overall survival figures were as of September 2013 and August 2014 and any subsequent time points alongside estimates of mean overall survival in PANO/BTZ/DEX and BTZ/DEX groups, respectively.

Response: *At data cut-off of September 2013, 286 deaths had occurred (134 [35%] in the panobinostat group and 152 [40%] in the placebo group), and median OS was 33.64 months (95% CI 31·34 to not estimable) in the panobinostat group versus 30·39 months (26.87 to not estimable) in the placebo group (HR 0.87, 95% CI 0.69 to 1·10; p = 0.26).*

As of the August 2014 data cut-off, 359 (86.5%) of the target 415 OS events had occurred: 169 in the panobinostat group and 190 in the control group. Of the 409 censored patients, 342 continued to be observed for survival data. Median OS was 38.24 months for the panobinostat group and 35.38 months for the control group (p = 0.1783).

Table 12 of the Submission provides figures based on the data cut-off of September 2013, except for the 2nd interim OS analysis (median survival figures of 38.24 months and 35.38 months in PANO/BTZ/DEX and BTZ/DEX groups, respectively), which is based on the data cut-off of 18 August 2014 (after 359 events, 86.5% complete). Please note that footnote 'b' under table 12 noted this.

Table 18 on page 82 and following text on page 83 also separates the data based on the data cut-off dates as above, correctly.

A12. **Priority Question**: Page 24 – the summary of the cost-effectiveness reports total survival for PANO/BTZ/DEX and BTZ/DEX groups of 3.57 years and 2.797 years, respectively, which equates to 42.84 and 33.56 months in the two groups. with respect to this data please clarify the following:

a. which approach has been used to estimate survival for the purposes of the cost-effectiveness calculations?

Response: *The mean survival was calculated as the area under the modelled (and extrapolated) overall survival curves. Discounted estimates are presented.*

b. why the mean survival used in the cost-effectiveness analysis for PANO/BTZ/DEX patients is greater than the reported median overall survival while the survival of BTZ/DEX patients used in the cost-

effectiveness analysis is lower than the median reported overall survival?

Response: *The following reasons contribute to these differences:*

In line with the modelled English clinical practice, post-progression survival in the model is based on a subset of the PANORAMA-1 population who received LEN/DEX as subsequent treatment.

In line with the modelled English clinical practice related to NICE TA 129 and the BTZ label, stopping rules were applied (at cycle 4 and cycle 8, per label) on the BTZ arm of the model which changes the course of the treatment when compared to the PANORMA-1 trial.

A13. Page 75 (table 17) of the submission details that the median time to response for patients achieving CR/nCR according to investigator assessment was the same as the lower bound of 95%[0.76 (0.76-0.95)]. Please could you confirm this is correct and explain why this might be the case? The same applies to the data for patients achieving PR according to investigator assessment box [1.41 (1.41-1.51)].

Response: *The time to CR/nCR was presented incorrectly in Table 17. The median time to CR/nCR in the PAN/BTZ/DEX arm (n=107) was 2.83 months (95% CI: 2.33 months, 3.19 months), and in the BTZ/DEX arm (n=60) was 3.09 months (95% CI: 2.33 months, 3.65 months).*

We are seeking advice from our statisticians on the time to PR data.

Please note that the median DoR data presented in table 17 for pts with nCR/CR, ≥ PR, and PR was correct and since has been published in EHA-3302 by P. Moreau, 2015[1]*.*

A14. **Priority Question**: Pages 75 to 78 (section 4.7.4) of the submission states that the mean time a patient remained treatment-free up to progression was 7.49 months in the PANO/BTZ/DEX group compared with 3.86 months in the BTZ/DEX group. For the mean survival data used in the cost-effective analysis please provide the mean time spent in the pre-progression state, no treatment state and the post-progression state for PANO/BTZ/DEX and BTZ/DEX groups, respectively.

Response: *Please see the requested values from the cost effectiveness analysis below in terms of life years and months (discounted):*

[1] *Available at: http://learningcenter.ehaweb.org/eha/2015/20th/100518/philippe.moreau.analysis.of.outcomes.by.response.for.patients.with.relapsed.or.html?f=l5550p16m3*

Life years	PANO/BTZ/DEX	BTZ/DEX
Pre-progression Tx	0.50	0.30
Off Treatment	0.70	0.20
LEN+DEX	1.15	1.15
POM+DEX / BSC	1.22	1.14
Total	**3.57**	**2.80**

Months	PANO/BTZ/DEX	BTZ/DEX
Pre-progression Tx	6.00	3.62
Off Treatment	8.45	2.44
LEN+DEX	13.76	13.77
POM+DEX / BSC	14.63	13.73
Total	**42.84**	**33.56**

It must be noted that the values presented in section 4.7.4 have been derived by a slightly different methodology (i.e., modified TWIST analysis[2]), in which treatment duration was censored for a patient if progression assessed by the Independent Review Committee occurred before the true treatment discontinuation[3].

Following common health economic modelling practice, in the cost-effectiveness model treatment duration was modelled independently from progression-free survival though.

A15. **Priority Question**: Please provide the Kaplan-Meier curve for overall survival for the whole sample in the PANORAMA-1 study (the equivalent of Figure 24, p. 89 for all patients in the study), together with the underlying data.

Response: *The requested curves are provided in Figure 21 and Figure 22 on page 83 and 84, respectively.*

A16. **Priority Question**: Page 104 (table 25) – please clarify how the overall survival comparisons between PANO/BTZ/DEX and LEN/DEX (for example 38.24 months or 3.2 years for PANO/BTZ/DEX based on the full population), relate to the figures for life years gained reported on page 25 (table 3c) (for example 2.288 years for PANO/BTZ/DEX based on full trial populations)?

Response: *38.24 months (or 3.2 years) is referring to the median overall survival of the full PANORAMA-1 trial population estimated by the Kaplan-Meier method. One can interpret this value as the expected time after which less than half of the population is still alive.*

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[2] *Zee B, et al. J Clin Oncol. 1998;16:2834-2839.*

[3] *In a modified TWIST analysis, progression-free survival (PFS) is partitioned into two parts: treatment period and treatment free period. For the treatment period, input data is defined as follows:*

- *End of treatment = min(PFS, treatment end date)*
- *Patients censored for PFS prior to end of treatment are considered censored for treatment period.*

2.288 years is referring the mean length of life that a PANO/BTZ/DEX patient with at least 2 lines of prior treatments including an IMiD and BTZ can expect to live. This value is estimated by the cost-effectiveness model.

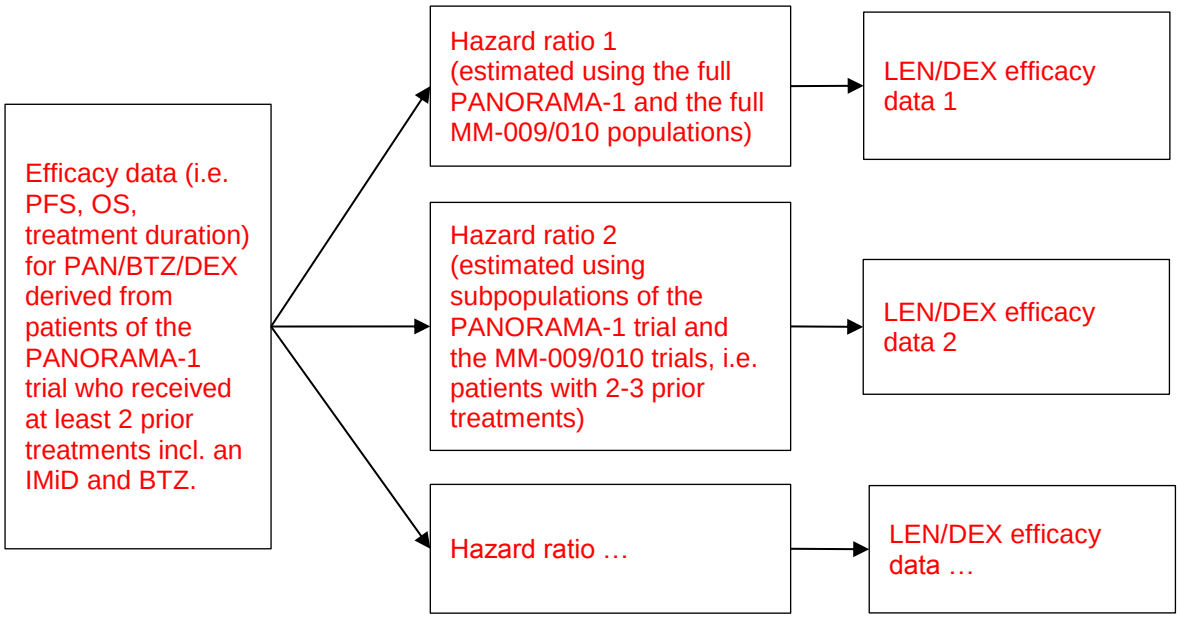
Clarification may be needed in terms of the populations used to obtain input parameters for the restricted population cost-effectiveness model:

- *Patients who received at least 2 prior treatments including an IMiD and BTZ: this is the population from which efficacy data are derived for the PANO/BTZ/DEX arm of the cost-effectiveness model. The use of this population remains the same irrespective of which indirect treatment comparison method is used to obtain hazard ratios for PFS and OS, that are subsequently applied to derive efficacy input parameters for LEN/DEX.*

- *Full PANORMA-1 trial population / patients with at least 2-3 prior treatments: these are the populations that were only used to obtain hazard ratios of PFS and OS (LEN/DEX versus PANO/BTZ/DEX). Hazard ratios were then applied to generate efficacy data for LEN/DEX in the model.*

Please see a visualisation of the modelling approach below in Figure 1.

Figure1 Modelling approach to obtain efficacy input parameters for LEN/DEX in the restricted patient population cost-effectiveness model (i.e. linking efficacy of LEN/DEX to efficacy of PANO/BTZ/DEX by applying hazard ratios)



A17. **Priority Question**: Page 105 (table 25a and b) – the progression-free and overall survival for the full population and the subpopulation with 2 to 3 prior lines of treatment, under the method of naïve comparison between PANO/BTZ/DEX

and LEN/DEX, are reported. Please clarify the corresponding figures for the other methods of comparison.

Response: *The requested values are provided in text boxes of figures for the:*

- *unadjusted Cox regression method: below Table 26*
- *matching adjusted indirect comparison: below Table 28*

Please see further clarifications above.

Section B: Clarification on cost-effectiveness data

B1. **Priority Question**: Please clarify why the Personal Social Services perspective has not been taken into account.

Response: *The personal social services perspective was considered but no particular aspects were identified for inclusion.*

B2. **Priority Question**: Please clarify how the searches for the cost-effectiveness data were carried out and explain why conference material was removed at the database search and then hand-searched. Please also confirm whether all published and unpublished trial data has been included.

Response: *Many cost-effectiveness abstracts are included in Embase and can be searched through Ovid but the entries retrieved do not include tables or figures included in the abstract and may not be indexed appropriately to be picked up in the search. Thus a more stringent method of retrieving congress abstracts is to hand-search the congress websites. This approach was used for this literature review. In order to reduce the number of duplicates between the electronic searches and the congress searches, congress abstracts were removed from the electronic search. Congress searches were limited to 2008 to present as earlier abstracts were considered to be of less relevance to the systematic review. Unpublished cost-effectiveness studies were not identified in the review.*

B3. **Priority Question**: The date limits of the study searches for the cost and economic data are inconsistent. On page 17 (section 8.11 of appendix) the searches were limited to 2003 whereas on pages 18 to 20 is limited to 2006 and on page 20 to 23, for the MEDLINE search the data is limited to 2003 until current on line 66 but on line 67 the dates are limited to 2006 until current time. Please indicate which is correct and carry out one of the following:

a. If the cost-effectiveness searches were carried out from 2006 onwards rather than 2003, please consider any conflict this has with the presentation of studies for this submission and/or any impact on the broader submission synthesis or impact on the model

b. If the searches were carried out from 2003 onwards please carry out your cost-effectiveness searches as presented on pages 18-23

(that is without the additional intervention terms you use in the 2013-2014 search) for the dates 2003-2006. This search will need to be screened to the same inclusion/exclusion criteria. Please highlight any new studies identified.

Response: *The initial searches in Embase and Medline were performed for 2006 onwards. Mention of 2003 on page 17 is an error. The initial plan was to perform all searches (clinical, humanistic and economic) for a 10-year time period (the systematic review was performed in 2013). However, given that the therapies of interest were not approved until 2004 (Velcade) and 2007 (Revlimid) or later, it was decided that a cut-off of 2006 would be more appropriate for the economic review. Indeed, the earliest relevant reference identified is the 2007 NICE submission for Velcade and the 2009 NICE submission for Revlimid was also identified. This confirms that the chosen time period can be expected to capture all evidence relevant to this submission.*

B4. Please clarify why the NHS EEDs database was only searched for studies published or indexed in 2014 when the database was updated until January 2015.

Response: *The last update to the Systematic Reviews was carried out in December 2014.*

B5. **Priority Question**: Page 148 (table 40) in the submission details that exponential functions have been used to model risk of progression and risk of death in those receiving BTZ/DEX who discontinue treatment without disease progression and those who receive LEN/DEX/last line of treatment. Please clarify why the same approach was not used for those receiving PANO/BTZ/DEX, those receiving BTZ/DEX in cycles 1-4 and BTZ/DEX responders in cycles 5-8?

Response: *The treatment pathway differed between the PANO/BTZ/DEX arm of the model and the BTZ/DEX arm of the model. Patients who initiated PANO/BTZ/DEX treatment, unlike the patients on the BTZ/DEX arm, were not subject to the stopping rules based on English clinical practice and the BTZ label, i.e. at the end of cycle 4 and cycle 8.*

Due to the small number of patients (cycle 1-4: n=18, cycle 5-8: n=14, see section 5.3.2) supposed to discontinue BTZ/DEX treatment without disease progression, the exponential model seemed to be the most plausible for modelling the risk of progression and death of these patients. Other models, including two or more parameters, were considered to be less reliable. Also, based on visual assessment, the exponential models fitted the Kaplan-Meier curves reasonably well.

B6. **Priority Question**: Page 151 (section 5.3.1) in the submission states:

'Transition probabilities for the risk of death in patients receiving LEN/DEX and the subsequent LLoT were derived from patient-level post-progression OS data from PANORAMA-1 for patients who received LEN/DEX as subsequent

antineoplastic treatment after PANO/BTZ/DEX or BTZ/DEX. Transition probabilities for LEN/DEX and LLoT were assumed to be the same for both treatment groups (ie patients initially receiving PANO/BTZ/DEX or BTZ/DEX)'.

It is then stated that:

'The risk of progression on LEN/DEX and the risk of post-progression death was assumed to be the same for both treatment groups (ie after PANO/BTZ/DEX and after BTZ/DEX) because no statistical difference between the treatment arms was established for post-progression death (see Appendix 16 for details). … Data for progression in patients receiving subsequent antineoplastic treatments after PANO/BTZ/DEX or BTZ/DEX was not collected in the PANORAMA-1 trial. Instead, the risk of progression or death on LEN/DEX treatment (or leaving LEN/DEX health state) was estimated using published data for PFS from the pooled MM-009 and MM-010 studies'.

Please clarify at what points in the clinical pathway data other than that from PANORAMA-1 is used to model progression and/or death and the assumptions being made about progression and/or death in the PANO/BTZ/DEX and BTZ/DEX groups, respectively.

Response: *While survival data was collected throughout the PANORAMA-1 trial, no progression data was collected beyond the study treatment progression, i.e. for post-progression treatments.*

The decision was made to make use of the trial data where available.

Risk of death while on subsequent antineoplastic treatment was derived from the PANORAMA-1 trial based on patient level data of those receiving LEN/DEX as the post progression treatment also to reflect UK clinical practice.

On the other hand, the risk of progression or death while on subsequent antineoplastic treatment was derived – in the absence of data from the PANORAMA-1 trial - from the published pivotal LEN/DEX trials (MM-009/010).

It was assumed that the risk of death and progression - while on subsequent antineoplastic therapy - was similar for all patients irrespective of the prior treatment (they received before the subsequent LEN/DEX treatment). This assumption was based on exploratory analyses investigating whether post-progression mortality should be differentiated for patients on the PANO/BTZ/DEX arm from patients on the BTZ/DEX arm. The results of the exploratory analyses are presented in Appendix 16 of the submission.

B7. **Priority Question**: Page 25 of main submission and pages 56 and 71 of appendix 17 - Please provide the cost-effectiveness ratio of PANO/BTZ/DEX compared with BTZ/DEX for the 2 subgroups.

Response: *The anticipated EMA label is as follows: "Farydak, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult*

patients with multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent."

In the setting evaluated in Appendix 17 in line with the above label of panobinostat, i.e. after at least 2 prior lines of treatment including an IMID and bortezomib, BTZ/DEX is not a valid comparator in the English clinical setting for the following reasons:

Bortezomib is not recommended beyond 2nd line use or after earlier use of bortezomib in the UK clinical practice currently.

- *NICE TA129[4] (October 2007) restricts the use of BTZ for patients who are at first relapse having received one prior therapy, i.e. for 2nd line use only.*
- *NICE TA228[5] (July 2011) recommends the use of BTZ as an option for the first-line treatment.*
- *NICE TA311[6] (April 2014) recommends the use of BTZ as an induction treatment of adults with previously untreated multiple myeloma.*
- *CDF[7] (Form ref: BOR1_v2.0) restricts the use of BTZ for patients with relapsed multiple myeloma who are bortezomib naïve.*
- *The BCSH guideline[8] recommends that treatment with lenalidomide (LEN) be considered for patients at second or subsequent relapse, or patients at first relapse who are intolerant of thalidomide or bortezomib.*
- *The draft National Chemotherapy Algorithm for Multiple Myeloma (v.0.7)[9] restricts the use of BTZ for patients who have not received prior bortezomib.*

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[4] National Institute for Health and Care Excellence. Technology Appraisal 129: Bortezomib monotherapy for relapsed multiple myeloma. October 2007. Available from: www.nice.org.uk/TA129. (Accessed 4 October 2013).

[5] National Institute for Health and Care Excellence. Technology Appraisal 228: Bortezomib and thalidomide for the first-line treatment of multiple myeloma. July 2011. Available from: https://www.nice.org.uk/guidance/ta228 (Accessed 5 June 2014).

[6] National Institute for Health and Care Excellence. Technology Appraisal 311: Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation. April 2014. Available from: www.nice.org.uk/TA311 (Accessed 4 October 2013).

[7] National Cancer Drugs Fund List. Version 4.0. 12 March 2015. Available from: http://www.england.nhs.uk/wp-content/uploads/2015/03/ncdf-list-mar-15.pdf (Accessed 14 April 2015).

[8] Bird JM, Owen RG, D'Sa S et al. Guidelines for the diagnosis and management of multiple myeloma 2014. Available from: http://www.bcshguidelines.com/documents/MYELOMA_GUIDELINE_Feb_2014_for_BCSH.pdf. (Accessed 4 June 2014).

[9] National Chemotherapy Algorithms. Multiple myeloma. Available from: https://www.engage.england.nhs.uk/consultation/specialised-services-consultation/user_uploads/chemothrpy-algrthms-mltpl-myeloma.pdf ; (Accessed 8 May 2015)

B8. **Priority Question**: Page 172 in the submission states that the health–related quality of life (HRQL) data notes that 'The cycle-specific mapped utility values were lower for PANO/BTZ/DEX than for BTZ/DEX at all time points, as expected from the differences in safety profile between the two treatments'. Please explain why the utility associated with the 'pre-progression, no-treatment' health state was mapped from the last HRQL assessment while still on treatment using **pooled data from both treatment groups**. If possible please separately report results using HRQL data while still on treatment for PANO/BTZ/DEX and BTZ/DEX groups.

Response: *With the lack of appropriate HRQOL data for the treatment free interval from the PANORAMA-1 trial, a proxy utility value was used for this period. While the choice of the proxy value inherently entails some arbitrariness, the following considerations were made:*

- *Acaster et al.[10] suggests a higher utility value is applicable to the treatment free interval as compared to the on-treatment period (prior to stopping therapy).*
- *Also, considering the treatment related adverse events associated with on treatment period, utility values for the pre-progression, no treatment health state (TFI) can be assumed to be higher than those of the pre-progression, on-treatment health states. It is acknowledged that the pre-progression, on-treatment utility values are lower for PANO/BTZ/DEX than for BTZ/DEX however applying a lower utility value for the off-treatment phase would be double counting the treatment-related adverse effects and as a consequence the related utility decrements.*
- *Should the utility values reflect the quality of response to treatments, assuming equal utility values while in the 'off-treatment pre-progression health state' could be considered conservative given the higher rate of CR/nCR on the PAN/BTZ/DEX arm compared to that of the BTZ/DEX arm.*
- *The approach of using the utility value associated with the last on-treatment cycle as the proxy for the treatment free interval also seems to be rather conservative.*
- *Two alternative utility values were considered during the design of the full PANORAMA-1 trial population cost-effectiveness model:*
    - *The utility mapped for patients at treatment initiation / screening: the estimated utility value was lower than the mapped mean utility value for BTZ/DEX. As a result, it could not be used.*
    - *Utility value of 0.720 associated with the TFI as reported in Acaster et al. Although this value is applied in the restricted population based*

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[10] Acaster S. et al. Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: a UK cross-sectional survey. Support Care Cancer. 2013 Feb;21(2):599-607

indirect treatment comparison (Appendix 17), it wasn't appropriate for the full population based analysis against BTZ/DEX as the mean 'on-treatment' utility value for the BTZ/DEX arm was mapped to be higher (0.725) than that.

In summary, it is acknowledged that the HRQOL of patients in the last treatment cycle was lower for PANO/BTZ/DEX than for BTZ/DEX however the purpose was not to take these values as their face value but rather to use them as a reasonable proxy for the off-treatment treatment phase. Scenario analyses investigated the impact of applying different off-treatment utility values.

B9. **Priority Question**: There are slight differences between cost reported in Table 58, section 5.5.3 (page 191) and section 5.5.2 (page 187), to which table 58 refers (for example, an average cost of £5,366 in the first treatment phase for PANO/BTZ/DEX in table 58 compared with £5,375 in section 5.5.2). Please confirm the unit costs used in the economic model.

Response: *The difference between the above costs (£5,366 vs £5,375) relates exclusively to the BTZ cost, more particularly to a difference in the average body surface of 0.01m^2 (i.e. 1.81m^2 vs 1.82m^2). Please note that in the full population model 1.81 m^2 (Section 5.5.2 of the main submission and 'Costs' sheet cell 'B31' in the full population model), while for the restricted population (i.e. after at least two prior lines including an IMID and BTZ) 1.82m^2 was used.*

Main submission:
Assuming the average body surface to be 1.81 m^2, the correct sentence under table 53 in section 5.5.2 should read as follows: "The average cycle cost was £5,366 and £1,837 in the first treatment phase and £4,562 and £918 in the second treatment phase for PANO/BTZ/DEX and BTZ/DEX, respectively."

Correspondingly, values in Table 55 should be as follows:

PANO/BTZ/DEX[11]	*£5,366 (first treatment phase, cycles 1 to 8)* *£4,562 (second treatment phase, cycles 9 to 16)*	*IV administration cost of £156 per treatment to be added for BTZ*
BTZ/DEX	*£1,837 (first treatment phase, cycles 1 to 8)* *£918 (second treatment phase, cycles 9 to 16)*	*IV administration cost of £156 per treatment to be added for BTZ*

Values presented in table 53, table 58 are correct.

[11] Based on the base case panobinostat price assumption of £776 for the 20mg capsule

Appendix 17

In table 16 and table 21 the values correspond to the above body surface (1.81m^2), however the correct sentence in section 1.5.2 under table 16 should read as follows: "The average cycle cost was £5,366 in the first treatment phase and £4,562 in the second treatment phase for PANO/BTZ/DEX."

Correspondingly, the values in table 18 should be as follows:

PAN/BTZ/DEX[a]	*£5,366 (first treatment phase, cycles 1 to 8)* *£4,562 (second treatment phase, cycles 9 to 16)*	*IV administration cost of £156 per treatment to be added for BTZ*

Correction in the model developed for the restricted population should be made in 'Costs' sheet, cell 'B41' (i.e. change from 1.82 to 1.81).

When further checking the cost inputs in the restricted population based model comparing PAN/BTZ/DEX with LEN/DEX, we recognised the following additional two mistakes:

1. *The administration cost (whether intravenous or subcutaneous) related to BTZ was wrongly calculated by being multiplied with the dose intensity of BTZ (75.8%).*

2. *3-weekly monitoring cost related to PAN/BTZ/DEX was wrongly calculated by double-counting the cost of the specialist visit (£156).*

*Please see in Table below the a) original and the b) correct cost data with the changes marked in **green**:*

a)

ORIGINAL CALCULATIONS for Restricted Population: at least 2 prior lines including an IMID and BTZ						
TREATMENT PHASE I			**Intravenous BTZ assumed**		**Subcutaneous BTZ assumed**	
Cost item	price	Nr / cycle (Phase 1)	Dose intensity (full population)	Cost	Dose intensity (full population)	Cost
PAN	£776.00	6	80.70%	£3,757.39	80.70%	£3,757.39
BTZ	£512.54	4	75.80%	£1,554.01	75.80%	£1,554.01
DEX	£7.80	8	87.50%	£54.60	87.50%	£54.60
IV	£156.00	4	75.80%	£472.99	0%	£0.00
SC	£25.00	4	0%	£0.00	75.80%	£75.80
AE costs	£136.85	1	100%	£136.85	100%	£136.85
Monitoring costs[1]	£341.56	1	100%	£341.56	100%	£341.56
				£6,317.41		£5,920.22
TREATMENT PHASE II			**Intravenous BTZ assumed**		**Subcutaneous BTZ assumed**	
Cost item	price	Nr / cycle (Phase 2)	Intensity (BC)	Cost	Intensity (updates)	Cost
PAN	£776.00	6	80.70%	£3,757.39	80.70%	£3,757.39
BTZ	£512.54	2	75.80%	£777.01	75.80%	£777.01
DEX	£7.80	4	87.50%	£27.30	87.50%	£27.30
IV	£156.00	2	75.80%	£236.50	0%	£0.00
SC	£25.00	2	0%	£0.00	75.80%	£37.90
AE costs	£136.85	1	100.00%	£136.85	100.00%	£136.85
Monitoring costs[1]	£341.56	1	100.00%	£341.56	100.00%	£341.56
				£5,276.61		£5,078.02

[1] see table below

Monitoring costs	Unit cost	Frequency per cycle	Cost
Serum protein assessment	£15.08	100%	£15.08
Skeletal survey (bone X-ray)	£75.00	6%	£4.33
Lab results - Haematology	£3.00	100%	£3.00
Lab results - Thyroid function test	£18.00	23%	£4.15
Lab results - Blood chemistry	£3.00	100%	£3.00
Specialist visit	£156.00	100%	£156.00
Additional visit	£156.00	100%	£156.00
Total			**£341.56**

b)

CORRECT CALCULATIONS for Restricted Population: at least 2 prior lines including an IMID and BTZ

TREATMENT PHASE I			Intravenous BTZ assumed		Subcutaneous BTZ assumed	
Cost item	price	Nr / cycle (Phase 1)	Dose intensity (full population)	Cost	Dose intensity (full population)	Cost
PAN	£776.00	6	80.70%	£3,757.39	80.70%	£3,757.39
BTZ	£512.54	4	75.80%	£1,554.01	75.80%	£1,554.01
DEX	£7.80	8	87.50%	£54.60	87.50%	£54.60
IV	£156.00	4	**100%**	**£624.00**	0%	£0.00
SC	£25.00	4	0%	£0.00	**100%**	**£100.00**
AE costs	£136.85	1	100%	£136.85	100%	£136.85
Monitoring costs[1]	**£185.56**	1	100%	**£185.56**	100%	**£185.56**
				£6,312.42		£5,788.42

TREATMENT PHASE II			Intravenous BTZ assumed		Subcutaneous BTZ assumed	
Cost item	price	Nr / cycle (Phase 2)	Intensity (BC)	Cost	Intensity (updates)	Cost
PAN	£776.00	6	80.70%	£3,757.39	80.70%	£3,757.39
BTZ	£512.54	2	75.80%	£777.01	75.80%	£777.01
DEX	£7.80	4	87.50%	£27.30	87.50%	£27.30
IV	£156.00	2	**100%**	**£312.00**	0%	£0.00
SC	£25.00	2	0%	£0.00	**100%**	**£50.00**
AE costs	£136.85	1	100%	£136.85	100%	£136.85
Monitoring costs[1]	**£185.56**	1	100%	**£185.56**	100%	**£185.56**
				£5,196.12		£4,934.12

[1] see table below

Monitoring costs	Unit cost	Frequency per cycle	Cost
Serum protein assessment	£15.08	100%	£15.08
Skeletal survey (bone X-ray)	£75.00	6%	£4.33
Lab results - Hematology	£3.00	100%	£3.00
Lab results - Thyroid function test	£18.00	23%	£4.15
Lab results - Blood chemistry	£3.00	100%	£3.00
Specialis visit	£156.00	100%	£156.00
Additional visit	£156.00	**0%**	**£0.00**
Total			**£185.56**

The above two mistakes can be corrected in the related CE model prepared for the restricted population (PAN/BTZ/DEX vs. LEN/DEX):

1. *The administration cost (whether intravenous or subcutaneous) related to BTZ was wrongly calculated by being multiplied with the dose intensity of BTZ (75.8%).*

    a. *'Treatment costs' sheet, cells E5 – E12 (referring to phase I of the PANORAMA-1 trial):*

The following wrong formula was used:
*=(B5*Costs!$W$18)+(C5*Costs!$W$19)+(D5*Costs!$W$20)+(C5*Costs!$W$48)*

Instead, the correct formula to be used:
*=(B5*Costs!$W$18)+(C5*Costs!$W$19)+(D5*Costs!$W$20)+(SUM('Treatment schedule'!$E$13:$E$33)*Costs!$W$48)*

(Cells E6-E12 should be changed correspondingly)

    b. *'Treatment costs' sheet, cells E13 – E26 (referring to phase II of the PANORAMA-1 trial):*

The following formula is used:
*=(B13*Costs!$W$18)+(C13*Costs!$W$19)+(D13*Costs!$W$20)+(C13*Costs!$W$48)*

Instead, the following formula is supposed to be used:
*=(B13*Costs!$W$18)+(C13*Costs!$W$19)+(D13*Costs!$W$20)+(SUM('Treatment schedule'!$E$50:$E$70)*Costs!$W$48)*

(Cells E14-E26 should be changed correspondingly)

2. *3-weekly monitoring cost related to PAN/BTZ/DEX was wrongly calculated by double-counting the cost of the specialist visit (£156).*

    a. *'Costs' sheet, cell W69:*

The following wrong formula was used:
=SUMPRODUCT(W62:W67,E70:E75)+W48

Instead, the correct formula to be used:
=SUMPRODUCT(W62:W67,E70:E75)

    b. *'Costs' sheet, cell W70:*

Because W70 depends on W69, W70 has to be changed as well:

The following wrong formula was used:
=(W69-W48)/2

Instead, the correct formula to be used:
=(W69)/2

In Appendix 17 among the limitations of the model based on the restricted population comparing PAN/BTZ/DEX with LEN/DEX we acknowledged that, with the absence of available subgroup data, we used the dose intensity applicable for the full trial population of the PANORAMA- trial as a proxy. Since the date of the submission we have acquired the dose intensity relevant to the specific subgroup under consideration.

The dose intensity applicable to the restricted population (after at least two prior treatments including an IMID and BTZ) are as follows:

PAN	***BTZ***	***DEX***
76.3%	*74.0%*	*79.8%*

Changes to the corresponding model (i.e. developed for the restricted population of after at least two prior lines including an IMID and BTZ) should be done on the 'Treatment Schedule' sheet in cells D8, E8 and F8 respectively.

The full data sheet on dose intensity representing the restricted subgroup (with at least 2 prior lines of treatment including an IMID and BTZ) is available in Appendix 18 at the bottom of this document.

The above two mistakes as well as the updated dose intensity have a significant impact on the ICER due to the small incremental QALY difference.

ICER per the two most plausible methodologies applied (discounted) with the corrected cost calculation and with the updated dose intensity assuming a) intravenous BTZ administration or b) subcutaneous BTZ administration:

a) Intravenous BTZ administration assumed

Methodology	***Technologies***	***Total costs (£)***	***Total LYG***	***Total QALYs***	***Incremental costs (£) versus LEN/DEX***	***Incremental LYG versus LEN/DEX***	***Incremental QALYs versus LEN/DEX***	***ICER (£) Cost per LYs gained[a]***	***ICER (£) Cost per QALYs gained[a]***
'MAIC' *deriving HRs from full trial populations*	*PANO/BTZ/DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*0.071*	*0.0295*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£148,567*	*2.216*	*1.491*					
'Unadjusted Cox' *deriving HRs from subpopulation (2 to 3 prior lines)*	*PANO/BTZ/DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*0.102*	*0.0518*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£147,632*	*2.186*	*1.469*					

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LYG, life years gained; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; QALYs, quality-adjusted life years

b) Subcutaneous BTZ administration assumed:

Methodology	***Technologies***	***Total costs (£)***	***Total LYG***	***Total QALYs***	***Incremental costs (£) versus LEN/DEX***	***Incremental LYG versus LEN/DEX***	***Incremental QALYs versus LEN/DEX***	***ICER (£) Cost per LYs gained[a]***	***ICER (£) Cost per QALYs gained[a]***
'MAIC' *deriving HRs from full trial populations*	*PANO/BTZ/DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*0.071*	*0.0295*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£148,567*	*2.216*	*1.491*					
'Unadjusted Cox' *deriving HRs from subpopulation (2 to 3 prior lines)*	*PANO/BTZ/DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*0.102*	*0.0518*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£147,632*	*2.186*	*1.469*					

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LYG, life years gained; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; QALYs, quality-adjusted life years

B10. **Priority Question**: Page 173 (paragraph 4) in the submission states 'No HRQL data from PANORAMA 1 were available for the post-progression health states. Instead, utility values published by van Agthoven et al were used…'. Please clarify whether the formal search was undertaken to identify studies reporting utility values and how the paper by van Agthoven et al. was selected?

Response: *A description of the design and results of the systematic literature review on health effects is provided in Appendix 15 of the submission dossier. In sum, the systematic literature review was designed to identify any utility values published for patients with relapsed / refractory multiple myeloma. Regrettably, no study was identified that reported on utility estimates in patients with relapsed / refractory multiple myeloma and therefore that could have been used for the panobinostat cost-effectiveness models. The findings of the systematic literature review were in line findings of previous systematic literature reviews that were part of prior NICE submission dossiers in relapsed / refractory multiple myeloma.*

The results of the systematic literature review suggested that the study of van Agthoven et al. was the only source that reported preference based utility estimates for patients with multiple myeloma. While these utility estimates were based on a treatment naïve patient population (The Dutch-Belgian Haemato-Oncology Cooperative Study Group trial), given the general lack of reliable utility estimates in multiple myeloma, the utility value reported for patients who did not respond to treatment (e.g. those patients who were still suffering from the effects of their disease) was assumed to be representative for patients post-progression in the panobinostat cost-effectiveness models. However, we considered the utility value reported by van Agthoven (0.810) and associated with pre-progression health state in various previous NICE appraisals in multiple myeloma to be inappropriate for this purpose. The utility values reported by van Agthoven were used in the two previous NICE appraisals (TA171, TA228).

B11. **Priority Question**: Page 193 (section 5.5.4, last paragraph) states that no indirect costs were included in management of adverse effects 'Only direct costs were taken into account and no differentiation was made between inpatient and outpatient management costs'. Please explain the rationale for not including indirect costs.

Response: *The exclusion of indirect costs in the models (not only for adverse events but also throughout the whole models) was based on the following considerations:*

- *Only one study was identified which reported indirect costs for management of MM.[12] This was an Italian study and reported costs according to phase of treatment – asymptomatic, receiving alloScT, symptomatic receiving pharmacotherapy or in plateau/remission. This cross-sectional study did not consider if patients were receiving first-line therapy or later lines of therapy.*

[12] *Petrucci MT, Calabrese E, Levi A et al. Cost of illness in patients with multiple myeloma in Italy: the CoMiM study. Tumori 2013;99:e193–202.*

This, plus the fact that costs related to Italy rather than the UK, meant that we considered the data were not robust enough to be considered in the model.

- *Previous NICE submissions in the relapsed / refractory multiple myeloma did not consider the incorporation of indirect costs.*

B12. Page 194 (section 5.5.5) - the submission states that '…it was assumed that 20% of the patients that die actually receive terminal care…'. Please clarify the rationale for using 20%.

Response: *In TA171 (2014), section 7.5.8, p180, the following description is provided: "…a multiple myeloma advisory board (Celgene Ltd; 20th June 2013, Golin Harris Offices, London) established that 20% of multiple myeloma patients are likely to require end of life care." Considering that the submitted panobinostat models represent a very similar setting, we have adopted these cost calculations.*

B13. Please clarify if and how the results of the PANORAMA-2 trial are incorporated into the model.

Response: *We confirm that the results of the PANORAMA-2 trial have not been incorporated into the submitted models.*

B14. **Priority Question:** Appendix 17, page 59 (table 27) of the submission, the life years gained and QALY results for PANO/BTZ/DEX under MAIC (for the comparison of PANO/BTZ/DEX and LEN/DEX) derive hazard ratios from full trial populations and Unadjusted Cox deriving HRs from the subpopulation (2 to 3 prior lines) appear to be identical. Please clarify the differences in the data sets used to model survival under MAIC full population and Unadjusted Cox subpopulation approaches.

Response: *HRs were generated for PFS and OS between the two treatments to inform on the modelled efficacy of the comparator in the treatment setting described by the restricted label of panobinostat, i.e. after at least 2 prior treatment including an IMID and BTZ.*

The above HRs were generated based on two sets of data available for both the PANORAMA-1 trial and the MM-009/MM-010 trials, that are the

a. *ITT dataset, and*

b. *The subpopulation from each trial with 2-3 prior lines of treatment.*

To provide a robust comparison and a reliable HR for both the PFS and the OS among the two treatment options, various methodologies were applied on both of the above data sets. These methods are described in detail in section 4.10 in the main submission as well as in Appendix 17.

Ultimately, it was assumed that the derived hazard ratios, irrespective of which of the two datasets they were derived from, can be used as proxies and therefore are applicable to the treatment setting described by the restricted label of panobinostat, i.e. patients with at least two prior lines of treatment including an IMiD and BTZ.

Section C: Textual clarifications and additional points

C1. **Priority Question**: please clarify the reason for not conducting a search for adverse events.

Response: *Novartis are aware of all the adverse event data for panobinostat and the relevant clinical trials covering comparator adverse events were all picked up in the efficacy search.*

C2. **Priority Question**: Please clarify whether the terms 'relapsed and refractory multiple myeloma' and 'multiple myeloma in people who have received at least one prior therapy' are being used interchangeably.

Response: *The PANORAMA-1 trial inclusion criteria were as follows:*
Patients with 1 to 3 prior lines of therapy who require retreatment of myeloma for one of the 2 conditions below:

a) *Relapsed, defined by disease that recurred in a patient that responded under a prior therapy, by reaching a MR or better, and had not progressed under this therapy nor up to 60 days of last dose of this therapy.*

b) *Relapsed-and-refractory to a therapy, provided that meets both conditions:*

   - *patient has relapsed to at least one prior line*
   - *and patient was refractory to another line (except BTZ), by either not reaching a MR, or progressed while under this therapy, or within 60 days of its last dose*

Hence the above terms are not fully interchangeable as being relapsed and refractory assumes at least two prior lines of treatment.

C3. **Priority Question**: Please clarify whether the terms 'subpopulation with prior ImiD and bortezomib and >= 2 prior lines of treatment' and 'subpopulations with 2 to 3 prior lines of treatment' are being used interchangeably.

Response: *No, they are not interchangeable subgroups.*

The latter is broader and includes patients with prior IMID and BTZ used as a combination treatment in 1st line setting.

Efficacy and safety analyses were performed for the above two subgroups differentiated by the type and the number of prior lines of treatment, ie patients who had received prior IMiD plus bortezomib (n = 193, 25% of the study population), and patients who had received prior IMiD plus bortezomib and ≥ 2 prior lines of treatment (n = 147, 19% of the study population). The 147 patients belonging to the more restricted population were all part of the less restricted population of 193 patients though.

C4. **Priority Question**: Please clarify the reasons for focussing the subgroup analysis on a comparison of PANO/BTZ.DEX relative to LEN/DEX in patients treated with 2 to 3 prior lines of therapy, rather than a comparison of PANO/BTZ/DEX with BTZ/DEX in the same subgroup.

Response: *The anticipated EMA label is as follows: "Farydak, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent."*

In the setting evaluated in Appendix 17 in line with the above label of panobinostat, i.e. after at least 2 prior lines of treatment including an IMID and bortezomib, BTZ/DEX is not a valid comparator in the English clinical setting for the following reasons:

Bortezomib is not recommended beyond 2nd line use or after earlier use of bortezomib in the UK clinical practice currently.

- *NICE TA129[13] (October 2007) restricts the use of BTZ for patients who are at first relapse having received one prior therapy, i.e. for 2nd line use only.*
- *NICE TA228[14] (July 2011) recommends the use of BTZ as an option for the first-line treatment.*
- *NICE TA311[15] (April 2014) recommends the use of BTZ as an induction treatment of adults with previously untreated multiple myeloma.*
- *CDF[16] (Form ref: BOR1_v2.0) restricts the use of BTZ for patients with relapsed multiple myeloma who are bortezomib naïve.*

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[13] National Institute for Health and Care Excellence. Technology Appraisal 129: Bortezomib monotherapy for relapsed multiple myeloma. October 2007. Available from: www.nice.org.uk/TA129. (Accessed 4 October 2013).

[14] National Institute for Health and Care Excellence. Technology Appraisal 228: Bortezomib and thalidomide for the first-line treatment of multiple myeloma. July 2011. Available from: https://www.nice.org.uk/guidance/ta228 (Accessed 5 June 2014).

[15] National Institute for Health and Care Excellence. Technology Appraisal 311: Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation. April 2014. Available from: www.nice.org.uk/TA311 (Accessed 4 October 2013).

- *The BCSH guideline[17] recommends that treatment with lenalidomide (LEN) be considered for patients at second or subsequent relapse, or patients at first relapse who are intolerant of thalidomide or bortezomib.*

- *The draft National Chemotherapy Algorithm for Multiple Myeloma (v.0.7)[18] restricts the use of BTZ for patients who have not received prior bortezomib.*

C5. Page 59 of the submission states that a planned second interim analysis was not performed. Please clarify why this was not performed and if it is to be performed, when it is planned.

Response: *The reasons for skipping the 2nd interim PFS analysis at 80% of the 460 progression-free survival events required are unknown to us; we are seeking advice from our statisticians as to why the interim analysis was omitted. However as indicated below, the final PFS analysis was performed and reported by San-Miguel et al in 2014 in Lancet.*

C6. Please confirm whether events for final progression-free survival and overall survival have been observed and if so please provide the data.

Response: *On page 59 the following sentence is misleading, and assumes the final PFS analysis has not been performed yet:*
"The final analysis for PFS ***is*** *to be performed when approximately 460 events have been observed in the full analysis set."*

In fact, the final PFS was performed at the data cut-off of September 2013 (Please see section 4.7.2 of the submission).

OS data have been reported for the 10 September 2013 data cut-off (first pre-planned interim analysis; corresponding to the final analysis for PFS) and for a data cut-off of 18 August 2014 (second interim OS analysis). Although the survival data from both analyses are not mature, both suggest a consistent numerical survival advantage for the panobinostat group (Table 18, section 4.7.6). The final analysis will be done after 415 deaths have been recorded.

C7. The submission states that CHMP opinion is due in May/June 2015. Please could you confirm whether this opinion has been received and if so please provide the wording.

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[16] National Cancer Drugs Fund List. Version 4.0. 12 March 2015. Available from: http://www.england.nhs.uk/wp-content/uploads/2015/03/ncdf-list-mar-15.pdf (Accessed 14 April 2015).
[17] Bird JM, Owen RG, D'Sa S et al. Guidelines for the diagnosis and management of multiple myeloma 2014. Available from: http://www.bcshguidelines.com/documents/MYELOMA_GUIDELINE_Feb_2014_for_BCSH.pdf. (Accessed 4 June 2014).
[18] National Chemotherapy Algorithms. Multiple myeloma. Available from: https://www.engage.england.nhs.uk/consultation/specialised-services-consultation/user_uploads/chemothrpy-algrthms-mltpl-myeloma.pdf ; (Accessed 8 May 2015)

Response: *The anticipated EMA label wording is as follows: "Farydak, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent."*
The above anticipated label is expected to become published on 26th June.

C8. Please consider lifting the confidentiality marking, for example the 'commercial in confidence' marking of the overall survival Kaplan-Meier data and post-progression curves in your company submission, to be in line with NICE processes. The NICE team will send you a more detailed request of items requiring consideration in due course.

Response: *Confidentiality markings have been lifted in most of the cases and documents have been re-submitted to NICE on 23rd June.*
The subgroup specific overall survival data is still marked as CiC though as this data is not yet final and has not been presented by Novartis.
Please note that final subgroup specific overall survival data is planned to be presented at the 57th ASH Congress in December this year should the number of events reach the required 415 in time for data submission.

Table IR47-37b (Page 1 of 2)
Dose intensity and relative dose intensity of study treatment component by treatment group
Safety Set - Subgroup- Prior IMiD and BTZ use and >=2 prior lines of therapy: Yes

	PAN+BTZ+Dex N=72			PBO+BTZ+Dex N=73		
	PAN	BTZ	Dex	PBO	BTZ	Dex
No. of patients receiving component - n (%)	72 (100.0)	72 (100.0)	72 (100.0)	73 (100.0)	73 (100.0)	73 (100.0)
Dose intensity [1]						
Mean	4.6	0.2	5.9	5.2	0.2	6.6
SD	1.36	0.06	1.99	1.01	0.05	1.55
Median	4.4	0.2	5.6	5.3	0.2	6.7
Minimum	2.4	0.1	3.0	3.1	0.1	3.1
Maximum	10.0	0.4	13.3	9.1	0.4	12.7
Relative dose intensity [2]						
Mean	76.3	74.0	79.8	87.2	82.0	88.4
SD	16.32	15.00	17.57	13.40	14.23	13.55
Median	76.3	72.5	83.3	91.6	84.5	93.1
Minimum	42.8	39.9	42.6	52.2	39.6	40.6
Maximum	100.0	101.5	106.1	102.1	101.5	102.1
Relative dose intensity categories - n (%)						
<50%	3 (4.2)	3 (4.2)	3 (4.2)	0	3 (4.1)	1 (1.4)
50 to <70%	22 (30.6)	28 (38.9)	21 (29.2)	8 (11.0)	12 (16.4)	7 (9.6)
70 to <90%	29 (40.3)	27 (37.5)	22 (30.6)	27 (37.0)	31 (42.5)	23 (31.5)

[1] Dose intensity = cumulative dose / sum of all actual cycle lengths; cumulative dose = total dose given during the study treatment exposure ; cycle length (except for last cycle)=(date of day 1 of next cycle – date of day 1 of current cycle);last cycle length =[date of last administration of study treatment component + X) – (day 1 of last cycle date)], where X is number of days remaining to complete exposure time of last dose of study treatment component or number of days from last administrated dose to next planned dose. Units: mg/day for PAN/PBO and Dex,mg/m2 day for BTZ
[2] Relative dose intensity(%) = 100*dose intensity / planned dose intensity

Table IR47-37b (Page 2 of 2)
Dose intensity and relative dose intensity of study treatment component by treatment group
Safety Set - Subgroup- Prior IMiD and BTZ use and >=2 prior lines of therapy: Yes

	PAN+BTZ+Dex N=72			PBO+BTZ+Dex N=73		
	PAN	BTZ	Dex	PBO	BTZ	Dex
90 to <110%	18 (25.0)	14 (19.4)	26 (36.1)	38 (52.1)	27 (37.0)	42 (57.5)
>=110%	0	0	0	0	0	0

[1] Dose intensity = cumulative dose / sum of all actual cycle lengths; cumulative dose = total dose given during the study treatment exposure ; cycle length (except for last cycle)=(date of day 1 of next cycle – date of day 1 of current cycle);last cycle length =[date of last administration of study treatment component + X) – (day 1 of last cycle date)], where X is number of days remaining to complete exposure time of last dose of study treatment component or number of days from last administrated dose to next planned dose. Units: mg/day for PAN/PBO and Dex,mg/m2 day for BTZ
[2] Relative dose intensity(%) = 100*dose intensity / planned dose intensity

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy [ID663]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]
Name of your organisation: Leukaemia CARE
Your position in the organisation: [redacted]
Brief description of the organisation:

Leukaemia CARE is a national charity; founded in 1967 and first registered with the Charity Commission in 1969; which exists to provide vital support services to patients, their families and carers during the difficult journey through the diagnosis and treatment of all forms of blood cancer (leukaemia, lymphoma; Hodgkin lymphoma; non-Hodgkin lymphoma; multiple myeloma; myelodysplastic syndrome; myeloproliferative disorders & aplastic anaemia).

Our current membership database stands at approximately 13,500 (this includes patients, carers and members of the patients immediate family members.)

Leukaemia CARE offers this support through its head office, based in Worcester and a network of volunteers all around the United Kingdom. Care and support is offered over seven key areas:

- 24-hour CARE Line and live chat (currently office hours only)
- Support groups
- Patient and carer conferences
- Nurse conferences
- One-to-one phone buddy support
- Cancer campaigning and patient advocacy
- Information and booklets

Since its inception over 25 years ago our CARE-Line has taken many thousands of calls from patients, their carers, family and friends. Our website provides extensive information on all aspects of the blood cancer journey, running from diagnosis to what happens when treatment stops and includes information on the emotional impact of a blood cancer and help for those caring for a patient. Our focus is purely on supporting anybody affected by a diagnosis of blood cancer, simply supporting a quality of life for all (see http://www.leukaemiacare.org.uk).

Leukaemia CARE also works with other charities and policy/decision makers to campaign for the rights of all patients affected by a cancer of the blood to have access to and receive the best possible treatment and care when they need it.

Organisational Funding:

Over 90% of our total funding come from our own fund raising activities, either via our members and fund raisers, legacies, grants, on-line shop, Christmas card sales, recycling exercises etc.

Leukaemia CARE receives funds from a wide range of Pharmaceutical companies, but in total those funds do not exceed more than 10% of our total income. The funds received from the Pharmaceutical Industry are received and dispersed strictly within the Guidelines as laid down by the ABPI Code of Practice 2015, Clause 27 - Relationships with Patient Organisations.[1]

We also operate strictly within the Guidelines defined by the "Leukaemia CARE Code of Practice."[2] This Code of Practice governing corporate funding is a commitment undertaken by Leukaemia CARE regarding our financial relationships with commercial entities and the pharmaceutical industry in particular. Both of these documents can be examined via the hyperlinks listed below, or they are available in hard copy upon request.

We pride ourselves on our independence from any external influence/undue pressure arising from any of the other stakeholder bodies operating within the same sphere of activity as ourselves – the Industry, the NHS, the DoH, NICE, the Medical Profession etc., all bodies that we work closely with but are independent from. We will maintain our independence to the best of our ability and eschew any support that could adversely impact our reputation. This fact is made clear to any drug company (or other body) seeking our advice/assistance at the time of first contact. Our Code of Practice is also shared with them at that time.

1 - http://www.pmcpa.org.uk/thecode/InteractiveCode2015/Pages/clause27.aspx
2 - http://www.leukaemiacare.org.uk/code-of-practice

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Myeloma (also known as multiple myeloma) is a rare, incurable, relapsing, remitting and relentless cancer which affects the plasma cells. Plasma cells are a type of white blood cell found in the bone marrow which produce antibodies called 'immunoglobulins' to help fight infections. Normally new plasma cells are produced to replace old cells, but in patients with myeloma, abnormal amounts of plasma cells are produced which only produce one type of antibody called 'paraprotein', which has no useful function and cannot fight infection effectively.

The majority of myeloma patients are over the age of 60, which may produce a range of complications and co-morbidities. Its multiple, complex mechanisms of action and this range of co-morbidities set it apart from almost every other cancer.

Symptoms of Myeloma

The most common symptom of myeloma is severe bone pain, frequently in the lower back, which is very disabling and means that patients' quality of life can be vastly reduced. Myeloma affects multiple places in the body (hence 'multiple' myeloma) where bone marrow is normally active in an adult i.e. within the bones of the spine, skull, pelvis, the rib cage, long bones of the arms and legs and the areas around the shoulders and hips.

Other common symptoms include:

1. Loss of appetite, feeling sick and constipation
2. Tiredness and lethargy
3. Weight loss
4. Unusual bruising and or bleeding
5. Frequent Infections
6. Kidney Problems

Collectively these symptoms can substantially impact on patients' quality of life. Myeloma patients experience a number of relapses and remissions, which require effective treatment at each stage. Moreover for most patients, living with myeloma can be very stressful and, at times, difficult to bear not just for the patients themselves but also their families, friends, carer's, employers, employees etc. In particular this includes feelings of shock/disbelief, denial, anger, fear/uncertainty, resentment, blame/guilt, isolation and depression. The

relapsing nature of myeloma can have a major impact on both the physical and psychological wellbeing of patients, which is particularly exaggerated by their awareness of the decreasing treatment options as the disease progresses.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

The most important considerations from the patient perspective will include survival (preferably long-term) and a better quality of life. It is important to note an improvement in quality of life is often considered to be as important to patients as improved survival (i.e. quality may be as important as quantity).

In addition to this, patients would consider an end to treatment or a prolonged treatment free interval to have a potentially huge positive impact on their quality of life. Another consideration for patients, their carers, friends and family is the knowledge that there may be access to effective further treatment options, should they relapse.

Whilst it must be acknowledged that patient populations are not homogeneous and making generalised statements of their preferences will always carry a certain degree of risk, we think it must be generally accepted that quality of life and survival, normally take precedence over other outcomes for all cancer patients (including myeloma patients).

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

The treatments for myeloma are varied and they all carry differing degrees of acceptability. Myeloma is a relentless, relapsing and remitting cancer and patients need to have effective treatments available at each relapse. All aspects of its management are underpinned by difficult treatment decisions, along with unpredictable side-effects and treatment outcomes. Historically, treatment options for myeloma were limited and survival prospects poor. However, after decades of limited research and innovation, the last ten years have seen a number of significant developments. It is important this progress does not stall and there is a continued effort to ensure that effective treatments are available at every relapse.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

The key benefits patients expect to gain from panobinostat are an improvement in progression-free survival and the potential for a prolonged treatment free period.

In addition to this panobinostat would increase the number of treatment options available to patients, ensuring more effective treatment options are available after each relapse. As mentioned above, the knowledge that there may be access to further effective treatment options, should they relapse, can have a huge impact on patients (and carers) emotional and physical wellbeing.

As outlined above, these are important considerations for patients who could potentially benefit hugely from availability of panobinostat.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Panobinostat is intended to be given alongside bortezomib and dexamethasone, where they are currently used in clinical practice. A clear improvement in progression-free survival has been demonstrated in this setting (versus bortezomib and dexamethasone alone).

If you know of any differences in opinion between patients or carers

about the benefits of the treatment being appraised, please tell us about them.

N/A

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

The treatment options currently available are a significant improvement on the historically available options, leading to recent improvement in outcomes for myeloma patients.

However, due to the relapsing, remitting, relentless nature of myeloma effective treatment options are required at each stage. As such, patients are always concerned about access to further effective treatment options, should their current treatments fail.

Please list any concerns patients or carers have about the treatment being appraised.

From the available clinical trial data there are potential worries about the side effect profile of panobinostat and particularly the increased number of adverse events.

However, it is important to note that numerous ‘trade-off’ studies have shown that some patients are willing to tolerate an increase in side-effects where there is a clearly demonstrated improvement in outcomes (e.g. progression-free survival in this case).

Therefore whilst panobinostat may not be a realistic treatment option for some patients, who may be unable to tolerate an increase in side effects, it appears to offer a significant improvement in progression-free survival for those who can tolerate it.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

N/A

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

N/A

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

N/A

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

✓ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

N/A

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

N/A

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

N/A

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies,

surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

This treatment may only be suitable for fitter patients who are able to tolerate the side effects. Where treatments are only suitable for fitter patients there is often reference to ‘age and fitness’ in the selection of patients’ treatment choices.

It is important to note that ageism is proscribed by the NHS and NICE and any reference to the suitability of patients for this treatment should be assessed in terms of clinical suitability alone. The availability of this treatment to patients should be determined by virtue of fitness alone, their age is irrelevant.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

As outlined above, by virtue of the increased side effect profile this treatment may only be suitable for fitter patients. We feel that it is important that the decision (whether the treatment is suitable) is left to clinicians and patients

who best placed to determine whether the individual patient would benefit from this treatment.

9. Other issues

Do you consider the treatment to be innovative?

✓ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Panobinostat belongs to a group of drugs known as histone deacetylase (HDAC) inhibitors, which is a new mechanism of action in this setting. As such panobinostat has the potential to offer a new type of treatment for patients in this setting where numerous options are needed.

Are there any other issues that you would like the Appraisal Committee to consider?

N/A

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

1. Myeloma is a rare, incurable, relapsing, remitting and relentless cancer.
2. Myeloma patients require effective treatment options at each stage of their disease.
3. An important consideration for patients, their carers, friends and family is the knowledge that there may be access to effective further treatment options, should they relapse.
4. Panobinostat is a new mechanism of action in this setting, offering patients an alternative to currently available treatments.
5. Panobinostat is a new treatment option for patients, which appears to offer a statistically and clinically significant improvement in progression-free survival for patients and the potential for a prolonged treatment free period.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy [ID663]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Myeloma UK

Your position in the organisation: [redacted]

Brief description of the organisation: Myeloma UK is the only organisation in the UK dealing exclusively with myeloma.

Our broad and innovative range of services cover every aspect of myeloma from providing information and support, to improving standards of treatment and care through research, education, campaigning and raising awareness.

We receive no Government funding and relying entirely on the fundraising efforts of our supporters and unrestricted educational grants from a range of pharmaceutical companies.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Myeloma is an incurable, complex and destructive cancer of plasma cells. There is currently no cure but treatment can halt its progress for varying periods of time and improve quality of life. Complications of myeloma include severe bone pain, bone fractures, fatigue, frequent infection and kidney damage, all of which can substantially impact on patients' quality of life.

Myeloma UK has recently conducted a number of surveys giving a detailed insight into how myeloma impacts on patients. Key points include:

- Due to fatigue (experienced by 58% of patients), patients struggle to carry out every day activities including having a shower and going to the toilet
- A depleted immune system (experienced by 30% of patients) also means that they are at constant risk of infection, which can often be severe or even fatal
- Four in five myeloma patients felt that side-effects affected them to some degree when on treatment, while around half said the side-effects experienced between treatments affect them to some degree
- 68% of myeloma patients report that they live with pain every day or on most days

A diagnosis of myeloma can have a major impact on the lives of patients. In a recent survey, one patient reported *"it made life very difficult as I live on my own and I was extremely ill".* Another commented *"when you are newly diagnosed, you feel so removed from reality. I felt as though I had been picked up and placed on an uninhabited island. I could see where I had come from, but I could not get back."*

Myeloma patients experience a number of relapses and remissions over the course of their disease and overtime their myeloma becomes resistant to currently available treatments. With each relapse, patients report that the disease takes its toll on their emotional and physical well-being. Treatment side-effects and frequent hospital visits also have social and practical impacts on patients' lives, including significant financial implications and reliance on a carer/family member for assistance with everyday tasks. Taken together, and alongside the emotional burden of a diagnosis of an incurable cancer, myeloma has a significant impact on the day-to-day lives of patients and their carers/families.

As myeloma is a relapsing and remitting cancer it is important that there are a range of novel treatments and treatment combinations are available at each stage for clinicians to prescribe to their patients at all stages of myeloma to allow flexibility and the optimal treatment of patients. It is also important that at each stage of their myeloma, patients receive the most clinically relevant treatment to prolong progression-free and overall survival.

Having panobinostat available for patients in the relapse setting, would add to the range of treatments available for doctors to use in their patients according to their individual disease with an aim of improving overall survival and quality of life in patients.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Myeloma patients and their carers inform us that they value treatments that put their myeloma into remission for a long-time and prolong their life. They also put a high degree of value on treatments that allow them to enjoy a normal day-to-day life and to spend time more time doing the things they enjoy, such as spending time with their family and leisure activities.

To inform our response to this NICE appraisal, Myeloma UK conducted seven informal Q&A with myeloma patients who received panobinostat through the Myeloma UK Clinical Trial Network (CTN) MUK *Six* trial.

When asked "What are your expectations when you start a new treatment?" Patients outlined that they wanted treatments that increased their remission and reduced their paraprotein to stable or non-detectable levels. This was combined with a hope that the remission was long-lived, although patients are aware that myeloma is incurable.

> *"I have no expectations. However, I have hopes that it will suppress or eliminate the myeloma."*
>
> *"When I start a new treatment, my expectations are that it will decrease my paraprotein and stabilise my disease."*
>
> *"I expect my disease to be put into a remission for a long time."*

They also have the expectation that treatments will have minimal impact on their quality of life – particularly little to no side-effects. Patients tell us that long-term side-effects, which persist after the termination of treatment, have a detrimental impact to their quality of life.

> *"I expect to have no side-effects, or be able to tolerate the side-effects very well, as this has always been the case with previous treatment with Velcade. I expect to be able to continue to work and to look after my family."*

The treatment outcomes valued the most are those to do with length and quality of life – progression free (PFS) and overall survival (OS).

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

As myeloma is a relapsing and remitting cancer, it is difficult to compare treatments in head-to-head terms as some patients may tolerate a treatment well and others may not. Patients may also benefit from a drug when used in combination with other drugs or when used at different stages of their disease.

Given the individual and heterogeneous nature of the disease, it is therefore important to have a range of treatments and treatment combinations available to ensure that doctors are able to treat their disease flexibly and improve outcomes.

Below we cover our experience of each of the comparators mentioned in the final scope for the appraisal. We cover the advantages and disadvantages of each. We cannot state which are preferred by patients, as this varies on a patient by patient basis.

The treatments that are approved in the relapse setting are acceptable to the majority of patients, however there is a continuous need to develop and bring new drugs and drug combinations to market that prolong progression-free and overall survival in myeloma. There is also a need to use NICE approved treatment in increasingly innovative ways.

Velcade

NICE guidance (TA129) recommends bortezomib monotherapy (Velcade®) as a treatment in patients at second line (first relapse), although clinical trial data and practice demonstrate its effectiveness at all stages of myeloma.

The efficacy of Velcade is greatly improved with the addition of a steroid (usually dexamethasone) and/or an alkylating agent (such as melphalan or cyclophosphamide). The APEX trial found that the number of patients experiencing a partial or complete response to myeloma rose from 40% to over 60% with the addition of dexamethasone.

Until recently it had been approved by the Cancer Drugs Fund (CDF) in England as a retreatment for myeloma patients in the relapsed setting. However, this is no longer available to patients.

As Velcade has been approved since 2007, doctors and patients have lengthy experience of administering and receiving the drug on the NHS.

Advantages

Most myeloma patients who receive Velcade outline that it is well tolerated and report an improvement in myeloma-related symptoms and complications, overall general health and quality of life. In the majority of patients, Velcade is effective at putting their myeloma into a quick remission and their side-effects are well managed.

Velcade is also very well tolerated in patients with impaired kidney function as a result of their myeloma, so it is a treatment of choice in these patients.

Velcade is given to patients in up to eight cycles, so it is a relatively short treatment frequency compared to other myeloma drugs which are given on a treat until disease progression basis. This allows patients to have treatment breaks, which are valued by patients.

Disadvantages

Some patients report that a number of the side-effects of Velcade are difficult to deal with and can be debilitating.

The most commonly reported side effect of Velcade is peripheral neuropathy (mild to severe tingling and numbness in the hands and feet), affecting up to 30% of patients. However, this has been greatly improved through the development of subcutaneous formation of the drug**.**
Other complications are anaemia, fatigue, skin rashes and gastrointestinal disturbances – although in the majority of cases these are appropriately managed by a health care professional.

As Velcade is given subcutaneously, it means that patients have to attend hospital in order to receive a treatment. This can be seen as a disadvantage in some cases as patients have to take the time out of their daily routine to attend day clinics.

However a patient preference survey conducted by Myeloma UK found that patients are divided in terms of preferences of how to receive treatment, with some patients preferring to attend day patient clinics as they get to meet other patients and receive treatment in a "safe" environment. They also get to see their healthcare team on a regular basis. This can therefore also be seen as an advantage, depending on the patient preference.

Revlimid
UK myeloma doctors are well used to prescribing Revlimid for patients at third line (second relapse), having received NICE approval in 2009. Revlimid is also currently being assessed by NICE as a treatment in second-line and is approved by the Cancer Drugs Fund in England in this setting.

Like Velcade, whilst it is approved as a treatment in second relapse, it is well known to be effective in all stages of myeloma.

<u>Advantages</u>
Patients report that Revlimid in combination with dexamethasone is very effective treatment and is an easy to take formulation, particularly given the tablet form which can be taken at home. As some patients can be on Revlimid in excess of two years, the tablet formation is better suited given the minimal impact it has on their lives. Although, as outlined above, patient preferences for where they want to receive their treatment can vary,

Myeloma UK sees and speaks to patients who respond well to Revlimid and it can be very effective in patients, keeping their disease at bay for long periods of time. It has a lesser side-effect profile than related immunomodulatory drugs such as thalidomide, particularly in terms of neuropathy.

Disadvantages

Side-effects of Revlimid include low blood counts and there is a risk of venous-thromboembolism and blood clots whilst taking the treatment. Patients also frequently report fatigue which impacts negatively on their quality of life and peripheral neuropathy, although this is a lesser risk than in thalidomide and Velcade. Another side effect is skin rashes.

As with other treatments these side effects can be largely mitigated or improved through appropriate management by a healthcare professional.

Revlimid is also given on a treat until progression basis, so patients do not have long treatment free breaks.

Other treatment combinations

In first and second relapse, thalidomide and other chemotherapy combinations are not commonly used as Velcade and Revlimid are NICE approved. It is more likely to be used as a salvage treatment or if a patient has had a very good response to thalidomide in the newly diagnosed setting – although patients will most commonly have Velcade so they do not miss out on their opportunity to access NICE guidance.

Thalidomide is an important back-bone drug in myeloma, and patients report it is well-tolerated and reduces the activity of the disease. Where thalidomide is used in the relapse setting, in most cases it will be used if a patient has previously had a good response to thalidomide so it is likely to be well tolerated again.

Thalidomide has a range of toxicities including thromboembolic events, blood clots and peripheral neuropathy.

Pomalidomide (Imnovid®) is another treatment licensed for patients in the relapsed setting at fourth line (third relapse), however, it has received negative guidance from NICE. It is currently funded through the Cancer Drugs Fund in England in combination with dexamethasone.

Patients report is it well tolerated and has a lesser side-effect profile than other immunomodulatory drugs, particularly with reduced cases of peripheral neuropathy and it is better tolerated by patients with kidney impairment.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Myeloma patients who have received panobinostat through the Panorma-1 trial and MUK *six* report that there are a number of advantages of panobinostat.

Different mechanism of action

Panobinostat is a first-in-class histone deacetylase (HDAC) inhibitor. A major advantage of panobinostat is that it offers an entirely new mechanism of action to other treatments that are approved for use in the disease.

Adding drugs with new mechanisms of action into treatment combinations can help to treat underlying myeloma clones, improving a patient's response to treatment.

Data published to date on PANORAMA-2 study has also highlighted that patients who have become refractory to Velcade, are able to respond again when given in combination with panobinostat.

Survival advantage

In the large Phase III trial, Panorama-1 and in preliminary MUK *six* data, there was a reported improvement in progression free survival (PFS) with the panobinostat, Velcade and dexamethasone combination. The data also shows an overall survival gain when panobinostat is added to the Velcade and dexamethasone combination.

This aligns with patient expectations of treatment, as panobinostat improves the length of remission and survival with myeloma.

The patient participants in MUK *six* that Myeloma UK communicated with in the lead up to the appraisal, all reported that receiving the panobinostat combination reduced their paraprotein and improved their quality of life.

When asked whether they thought panobinostat should be made available to patients on the NHS, they replied:

> *"Yes, most definitely. It has proved to be a very effective treatment combination, particularly if it helps to stabilise the myeloma."*
>
> *"Yes. It gave me approximately six months of considerably reduced symptoms and improved my quality of life with relatively few side-effects."*
>
> *"Yes, it helped me. We need a wide variety of drugs available to fight myeloma."*
>
> *"Yes. I was impressed by the way it lowered my paraprotein so fast. I was told if I had received a reduced dose outside of the trial, I would have experienced fewer side-effects. If my remission lasts for a lot longer, I will give full credit to panobinostat for this. I think it should be an option for patients whose disease is resistant to other treatments."*
>
> *"Yes. From my experience no other treatment has worked except panobinostat."*

Improved myeloma symptoms

Patients report that one of the main advantages of panobinostat is that it improves symptoms associated with myeloma and their quality of life in the longer term.

Myeloma patients in the MUK *six* trial were asked about the symptoms related to their myeloma they were experiencing prior to receiving the panobinostat treatment. Patients reported neuropathy, fatigue, bone pain, breathlessness, difficulty walking and fatigue. They were then asked to describe the impact that panobinostat treatment had on the symptoms described. One patient outlined that it reduced their symptoms entirely, four patients reported that it reduced their symptoms significantly, one patient reported their symptoms reduced partially and another said it had no impact at all.

Treatment formulation

Patients report that the oral formulation of panobinostat drug is easy and convenient to take.

We know from a recent Myeloma UK survey that some patients would prefer to have a treatment that they could receive at home (preferably in tablet form) due to ease, convenience, the fact it reduces hospital visits and allows patients to avoid invasive procedures such as infusions.

Whilst panobinostat is an oral treatment a potential disadvantage is that Velcade when it is administered either subcutaneously or intravenously it requires a visit to the hospital either once or twice a week during the treatment cycle (depending on the dose the patient receives).

However, in the same survey mentioned above, some patients reported that they preferred treatments which allow them regular visits to the hospital as it gives them confidence in the quality of care and means that there is medical support available when they are receiving their treatment. Some patients also reported problems with committing to oral dosing schedules.

With the seven patients that we interviewed the majority of patients were happy with how they received the treatment.

Treatment duration

Patients report that the treatment duration of panobinostat is acceptable to them. It is not a treat until progression basis, so they can expect a treatment free interval at the end of treatment cycles where their disease has responded.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

See comments above.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

No comments

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

See comments above

Please list any concerns patients or carers have about the treatment being appraised.

Side effects

The main reported side effects of panobinostat combination treatment are gastrointestinal problems, in particular diarrhoea. Diarrhoea can impact negatively on patient quality of life and on patient's ability to leave their house on a daily basis.

Other side effects include neuropathy, fatigue, low blood counts and nausea. These are similar to the side-effects patients experience with other myeloma treatments and they are therefore able to tolerate them well.

However, patients and doctors report that these have been adequately managed through communication and supportive care.

In the small sample patients of patients Myeloma UK spoke to, five out of seven patients stated that they felt that their side-effects were fully managed by their healthcare professional and one patient felt they were partially managed. Four patients stated that the side-effects they experienced did not impact on their ability to carry out day-to-day activities, two stated it partially impacted on their ability to carry out day-to-day activities

and one patient outlined that it entirely stopped them from conducting day-to-day activities.

The patient who was unable to conduct day-to-day activities experienced severe side-effects and was withdrawn from the trial – despite it reducing their paraprotein to almost undetectable levels. The patient felt that if they had received the treatment out with the clinical trial, the doctor would have had more ability to reduce the dose to more manageable levels and would have been able to tolerate it better.

Unlike thalidomide and Revlimid, patients receiving treatment with panobinostat are not at risk of thromboembolism.

Neuropathy associated with Velcade

As mentioned above, 30% of patients who receive Velcade experience mild to severe peripheral neuropathy. Patients report that neuropathy is one of the hardest symptoms to live with.

However, bortezomib has recently been granted its licence to be provided subcutaneously, which is associated with less debilitating side-effects and in particular reduces the level of peripheral neuropathy in the patient's experience.

Panobinostat is not associated with increased neurotoxicity, so will not increase risk of any neuropathy.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

No comments

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

No comments

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

No comments

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

X Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Panobinostat is not been used on the NHS aside from on clinical trials. We therefore cannot answer this question. Dose adjustments to counter for patients who experience severe side-effects are easier in clinical practice than in trials, so this will have a positive impact on patient experience.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes. The trial outcomes of PFS and OS are very important to patients.

Information on quality of life is also very important, as there is often a trade-off between length of life and side-effects/complications experienced.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

No comments

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

No comments

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

No comments

9. Other issues

Do you consider the treatment to be innovative?

x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

As outlined above, panobinostat is the first-in-class HDAC inhibitor and has an entirely new method of action to the backbone myeloma treatments such as IMiDs and proteasome inhibitors. It works by blocking the action of histone deacetylase in myeloma cells, preventing their growth and survival.

Through offering this additional mechanism of action, it can offer innovation when added into already existing treatment combinations such as Velcade and dexamethasone, as it

can help kill underlying clones in myeloma – increasing the length of remission that patients experience and in turn their overall survival.

Panobinostat can also help patients respond to Velcade, where they have previously been refractory and is effective as a maintenance

Are there any other issues that you would like the Appraisal Committee to consider?

No comments

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Panobinostat should be made routinely available to patients on the NHS, as it offers an entirely new mechanism of action to other myeloma treatments. This is a valuable addition to the treatment combinations used in myeloma and offers a multifaceted attack on the underlying myeloma clones

- Clinical evidence and patient level information shows that panobinostat combination treatment is very effective in increasing progression free and overall survival in myeloma patients. Alongside an increased quality of life, these are the two outcomes that patients value the most

- Patients who have received panobinostat report a good experience with the drug. The side-effects are well-tolerated and it treats and reduces the underlying symptoms of myeloma thus improving patients quality of life and their ability to carry-out normal day-to-day tasks

- The treatment duration and administration of panobinostat are acceptable to patients

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy [ID663]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisations: Royal College of Pathologists
UK Myeloma Forum

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **Yes**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? **Yes**
- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy [ID663]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Response

The technology is not available at the current time, except under a compassionate use “Named Patient Supply” programme run by the company. This programme is relatively new and is unlikely to been much used.

Outside of clinical trials, patients with relapsed myeloma are treated with a Bortezomib-based regimen at first relapse, as per NICE guidance TA129, and with Lenalidomide at second relapse, again, as per NICE guidance TA171. Patients who did not receive Bortezomib at first relapse are able to receive it at subsequent relapse, under the Cancer Drugs Fund. At third and subsequent relapse, patients are treated with a variety of therapies, including Pomalidomide, Bendamustine, Thalidomide and alkylating agents (melphalan, cyclophosphamide). There is no specific guidance relating to treatment at this stage of the pathway for these patients.

The technology is likely to be used in circumstances where Bortezomib and Dexamethasone are used, i.e. in patients with relapsed myeloma who have received one, or two prior therapies. There are no great geographical variations in clinical practice, apart from the access to clinical trials that are available to patients being treated at large centres or teaching hospitals. The technology should be used in specialist clinics in tertiary care, and is oral, so does not have other additional requirements for administration.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy [ID663]

Clinical guidelines are the 2011 BCSH Guidelines (available on the BCSH Website) along with an update published in 2014. These clearly do not consider the technology and it is likely that a further update will be issued in due course.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Response

The technology has the advantage of being oral, and hence convenient. Unlike other therapies available for treating myeloma patients (thalidomide, lenalidomide), it is not associated with an increased risk of thrombo-embolism, and so no precautions need be taken in this respect. Unlike the commonly used therapies, bortezomib and thalidomide, the technology (Panobinostat) is not associated with neurotoxicity, and this is an advantage. One disadvantage of the technology is are the side effects of diarrhoea, nausea and fatigue, that are seen when used in combination with bortezomib and dexamethasone.

Disease responses to the combination, bortezomib, dexamethasone and panobinostat will be monitored in the same way as for other anti-myeloma therapies, and in case of lack of response, treatment will be discontinued.

I was an investigator on the phase 3 study, Panorama 1, that has produced the data on which application for licence is being currently based. I am therefore familiar with the toxicity profile of the technology, and can confirm that clinical circumstances of

the trial are reflective of current UK practice. It is important that the trial had a positive outcome and met its primary endpoint of progression-free survival (PFS). For patients with relapsed myeloma, PFS benefit is a valid measure of long term benefit. The trial also demonstrated a significant increase in overall response rate, and a more striking increase in the rate of complete response, which indicates that the technology is able to produce higher quality and deeper responses when compared to the control (comparator) arm of bortezomib and dexamethasone. Depth of response is currently considered to be a valid surrogate marker for long term benefit.

The main toxicity relates to gastro-intestinal effects, that can largely be managed with good patient education, careful monitoring of patients, prompt use of supportive medication and dose and regimen adjustment for toxicity, or in case of older patients, such as those above the age of 75 years.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Response
In the UK, we have carried out the phase 2 study of Panobinostat, Bortezomib, Dexamethasone and Thalidomide in patients with relapsed myeloma (similar patient group to the phase 3 study, Panorama 1). This is a Myeloma UK Clinical Trial Network study that is fully recruited, and preliminary results were presented at the Annual meeting of the American Society of Haematology in December 2014. We have observed a high response rate to this combination (approximately 80%) and importantly, investigators found the toxicity profile manageable with maintenance of response despite dose adjustments. These trial data may well be helpful for the appraisal committee.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Response
The only effect on the delivery of care for these patients would be the need to provide information regarding possible side effects (as is the case with any new treatment) and training of health care professionals with regard to the toxicity profile. No additional facilities or equipment are required.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Response
Not applicable

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Guy Pratt

Name of your organisation

1) Heart of England NHS Foundation Trust
2) University of Birmingham

Are you (tick all that apply):

✓ Yes I am a specialist in the treatment of people with the condition for which NICE is considering this technology?

✓ Yes I am specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?

I am a member of the UK myeloma Forum and lead for guideline development and also clinical lead for the NICE myeloma guideline due to be published in 2016

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Patients with myeloma are often enrolled into a clinical trial at diagnosis. If not patients are treated most commonly with either a bortezomib regimen or thalidomide regimen. Both have NICE TAs associated with them. Currently there is no access to lenalidomide regimen but this will be looked at by a NICE TA and may change.
Younger, fitter patients if suitable will proceed to an autologous stem cell transplant.

The treatment at relapse is complicated and depends on a number of factors including duration of response, previous tolerability, frailty, comorbidities, availability of a suitable trial etc...There is a TA allowing bortezomib treatment at this point. Some patients may have a second autologous stem cell transplant

Yes there may be some geographical variation in particular as regards access to trials but overall treatment broadly follows the TAs in the UK

Yes there is some differences in opinion especially as there is a complete lack of evidence in some areas. In particular the main two groups of drugs the proteasome inhibitors ie bortezomib and the immunomodulatory drugs ie lenaldiomide have not been compared head to head in any study

There is huge variability in patient response and survival and an increasing interest in genetic subgroups but as yet this has not impacted in the UK as to how we treat patients as there is a lack of clinical trials in this area and a need for more data.

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Single Technology Appraisal (STA)

Therefore as yet no subgroups of patients have been identified who may or may not benefit from panobinostat.

Myeloma is still incurable so any new agent with any efficacy is important to assess. The evidence for a new agent is always initially in the relapsed setting so that's where it gets introduced. It is harder to show efficacy in patients with multiply relapsed disease as the disease is much less responsive to treatment then. However because the evidence accumulates first in this setting it does not mean that this is the best place for the drug and it always needs looking at in other settings. Dugs typically show synergy so combination regimens are likely to be more efficacious than single agent although at the same time toxicity will increase. Panobinostat has very limited activity given as a single agent.
In the largest trial PANORAMA 1 Bortezomib +dexamethasone + vorinostat was compared to Bortezomib +dexamethasone so it is likely this will be the comparator in this appraisal
It is extremely difficult to talk about comparators in relapsed myeloma as there are multiple agents and even more combinations of these with newer drugs in the pipeline such as daratumumab and ixazomib so any new agent will immediately get added to a combination.

Clinical guidelines have not covered panobinostat as far as I am aware as there is limited data that has only recently been published.

It is not being used outside of clinical trials in the NHS and never outside of Haematology departments

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

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Single Technology Appraisal (STA)

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

It is a tablet which is given in addition to Bortezomib +dexamethasone

The disadvantages of the technology are side effects– diarrhoea, nausea and bone marrow suppression are the major side effects and cost obviously

Patient will be monitored as before with each cycle of therapy so no extra visits. There are documented protocols for managing toxicity

I have some concern that although there is an improvement in progression free survival that the effect on overall survival is less clear

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

No issues relating to equality and diversity

Any additional sources of evidence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Not that I am aware of

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

It is a simple tablet so will not impact on Haematology units massively as follow up intervals will not be changed. Some education will be needed as regards side effects and managing toxicities and there will inevitably be some increased toxicity compared to Bortezomib +dexamethasone alone.

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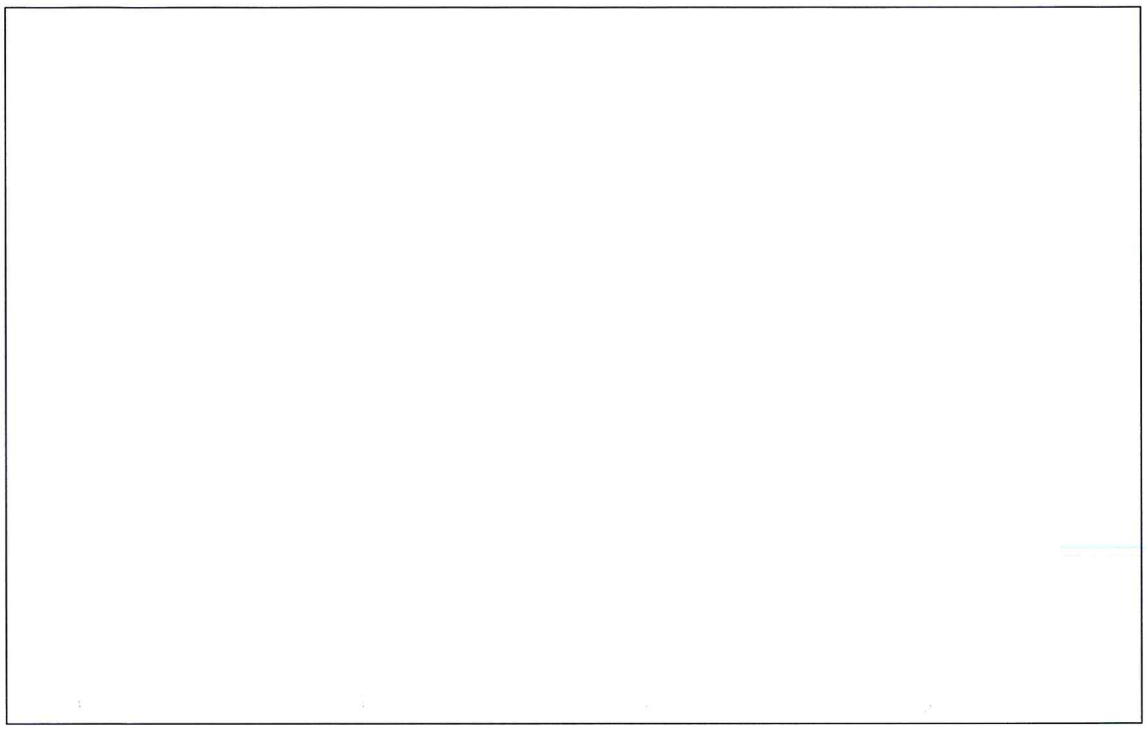
Single Technology Appraisal (STA)



NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Professor Jamie Cavenagh

Name of your organisation : Barts Health NHS Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **YES**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **YES: LEAD CONSULTANT IN THIS AREA**
- other? (please specify)

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Outside of clinical trials, the majority of MM patients throughout the UK will be treated with Bortezomib-based therapy at the time of first relapse and Lenalidomide-based therapy at the time of second relapse. Thereafter, patients are likely to be treated with a number of different therapies including Pomalidomide and Bendamustine. I suspect that this treatment pathway is commonly followed, not least because of prior NICE funding approvals.

Given the PANORAMA-1 Trial data, I suspect that Bortezomib/Dexamethasone/ Panobinostat ('BDP') will likely be used in circumstances where Bortezomib/Dexamethasone ('BD') is currently used.

Currently, there are no data to suggest that particular patient subgroups benefit from this treatment but further analysis of the PANORAMA-1 dataset may reveal such differences. It is important to bear in mind that these would be unplanned subset analyses which present potential biases.

BDP will be used in MM specialist clinics and will involve clinicians, specialist nurses and pharmacists.

The technology is not currently available.

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Single Technology Appraisal (STA)

The current UK Guidelines are the 2011 BCSH Guidelines (available on the BCSH Website) along with updates. These clearly do not consider BDP and it is likely that a further update will be issued in due course.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

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Single Technology Appraisal (STA)

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

As stated, I suspect that BDP will be considered for patients who would currently receive BD treatment. BDP will be pretty much equivalent to BD in terms of ease of administration.

BDP will likely be discontinued in the same way as any other MM treatment, namely in the presence of progressive disease or intolerance.

I was an investigator in the PANORAMA-1 clinical trial and can confirm that the patients treated by myself were representative of UK MM patients. Therefore, I believe that the trials results can indeed be extrapolated to current UK practice.

For clinical trials with relapsed MM, progression-free survival is a widely accepted end-point and this was the primary end-point of the trial.

Panobinostat is not without a side-effect profile and this is dominated by gastro-intestinal effects such as nausea, vomiting and diarrhoea. There is subset of patients who will experience these and find them difficult to tolerate. However, with appropriate supportive management, the majority of patients will tolerate BDP.

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Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Not applicable.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I am the Chief Investigator of a Myeloma UK Clinical trial (MUK-6). This is a fully recruited Phase I/II Trial investigating the combination of Bortezomib, thalidomide, dexamethasone and panobinostat (VTD-Pano) in relapsed MM patients. Interim results have been presented at the 2014 ASH meeting and I will attach the poster.

We have observed a high response rate to this combination (approximately 80%) and the toxicity profile has been favourable. I think that this trial data may well be helpful for the appraisal committee.

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Single Technology Appraisal (STA)

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

As already said, I suspect that BDP would likely be used in the same circumstances where BD is currently being used. There would be minimal additional training or education required and no extra resources.

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Single Technology Appraisal (STA)

Appendix K – patient expert statement declaration form

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Single Technology Appraisal (STA)

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy [ID663]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Myeloma UK and consequently I will not be submitting a personal statement.

Name: Eric Law

Signed: [redacted]

Date: 31/07/15

Appendix K – patient expert statement declaration form

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy [ID663]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Myeloma UK and consequently I will not be submitting a personal statement.

Name: Stuart Fullerton

Signed: 

Date: 13/7/15

Panobinostat (Farydak®) for treating multiple myeloma in people who have received at least one prior therapy

A critique of the submission from Novartis

Report commissioned by:

NHS R&D HTA Programme

On behalf of:

NICE

Produced by:

Optimity Advisors
Peninsula Technology Assessment Group (PenTAG)

Although Optimity Advisors are primarily responsible for the work in this report, PenTAG retains responsibility for the standard of the report and the quality of the advice that it contains.

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Declaration of competing interest of the authors

None

Rider of responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows

Durand A, Rtveladze K, Pritchard C, Cooper C, Mujica-Mota R. The clinical and cost-effectiveness of panobinostat for treating multiple myeloma in people received at least one prior therapy. Single Technology Appraisal NIHR HTA Programme, Optimity Advisors and Peninsula Technology Assessment Group, 2015.

Contribution of authors

Adeline Durand: Contributed to project management, the critique of the company's submission, report writing and editing.
Ketevan Rtveladze: Contributed to the critique of the company's submission, report writing and editing.
Clive Pritchard: Contributed to the critique of the company's submission, report writing and editing.
Chris Cooper: Commented on the searches provided by the company and contributed to report writing.
Ruben Mujica-Mota: Contributed to the critique of the company's submission and commented on drafts of the report and is the guarantor of the report from PenTAG.

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Date completed:

July 2015

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List of abbreviations

AE	Adverse event
AIC	Akaike information criterion
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplantation
ASH	American Society of Hematology
BCSH	British Committee for Standards in Haematology
BIC	Bayesian information criterion
BNF	British National Formulary
BTZ	bortezomib
CF	Cognitive Functioning
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CR	complete response
CSR	Clinical Study Report
CTD	cyclophosphamide, thalidomide and dexamethasone
DAC	deacetylases
DEX	dexamethasone
DOX	doxorubicin
EBMT	European Group for Blood and Bone Marrow Transplant
ECG,	electrocardiogram
EF	Emotional Functioning
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	5-dimension EuroQol questionnaire
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
GHS	Global Health Status
GOG	Gynecologic Oncology Group
HDAC	histone deacetylase
HERC	Health Economics Research Centre
HMRN	Haematological Malignancy Research Network
HR	hazard ratio
HRQL	health-related quality of life
HSP	heat shock protein
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IQR	interquartile range

IRC	Independent Review Committee
LEN	lenalidomide
LLoT	last line of treatment
MAIC	matching adjusted indirect treatment comparison
mEBMT	modified European Group for Blood and Bone Marrow Transplant
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma
MR	minimal response
MRU	Medical Resource Utilisation
NCDF	National Cancer Drugs Fund
nCR	near-complete response
NICE	National Institute for Health and Care Excellence
Ntx	Neurotoxicity
ODAC	Oncologic Drugs Advisory Committee
ORR	overall/objective response rate
OS	overall survival
PANO	panobinostat
PANORAMA	PANobinostat ORAl in multiple MyelomA
PAS	Patient Access Scheme
PBO	placebo
PF	Physical Functioning
PFS	progression-free survival
PI	proteasome inhibitor
POM	pomalidomide
PR	partial response
QALY	quality-adjusted life years
QLQ-C30	Quality of Life Questionnaire-core 30
QLQ-MY20	EORTC MM-specific module
QTcF	QT interval corrected for heart rate by use of Fridericia's QT formula
RCT	randomised controlled trial
RF	Role Functioning
rrMM	relapsed/refractory MM
SD	standard deviation
SF	Social Functioning
SMC	Scottish Medicines Consortium
STA	Single Technology Appraisal
TA	Technology Appraisal
TFI	treatment-free interval
THAL	thalidomide
TTP	time to progression
VBA	Visual Basic for Applications

1. Summary

The text cited directly from the submission by Novartis (hereafter referred to as "the submission") is presented with quotation marks in italic and cross referenced. Note that the specific sections/pages of the submission referred to by the ERG in this report apply to v0.2 of the submission. In addition, the ERG reviewed the economic analysis presented in the Appendix 17 of the submission.

Given the nature of the STA process, the ERG was bound to time constraints. Most of the initial review process was dedicated to finding the methodological and logical errors in the submission and its' Appendix 17. Some updated figures were submitted by the company during the clarification stage.

1.1. Scope of the submission

The submission from Novartis considered the use of panobinostat (Farydak®) in combination with, bortezomib and dexamethasone for people with multiple myeloma who have received at least 1 prior therapy (PANO/BTZ/DEX). The comparator considered was bortezomib and dexamethasone ((placebo)/BTZ/DEX).

Novartis also considered in the Appendix 17 of the submission the use of PANO/BTZ/DEX triplet for patients with relapsed and refractory multiple myeloma who had at least two prior lines of treatment including immunomodulatory drug (IMiD) and BTZ based regimens. The comparator for this analysis was lenalidomide in combination with dexamethasone (LEN/DEX).

1.2. Summary of submitted clinical effectiveness evidence

The clinical effectiveness evidence of the submission is based on the PANORAMA-1 trial that is a phase 3, multicentre, randomised, double-blind, placebo-controlled study in patients with rrMM who have received between one and three prior treatment regimens. In this trial patients received either the triplet therapy PANO/BTZ/DEX or BTZ/DEX. The primary efficacy endpoint of the trial was progression free survival. An extension of 3.9 months was demonstrated (according to investigator assessment). The secondary efficacy endpoints include overall survival, response rate, response duration and time to progression. No mature overall survival results are presented in the submission.

The clinical effectiveness evidence for patients who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen relies on indirect comparison of the PANORAMA-1 trial (the intervention arm) and the pooled data from MM-009 and MM-010 trials for LEN/DEX. The indirect treatment methodology used to estimate the relative effectiveness between PANO/BTZ/DEX and LEN/DEX treatments was the Unadjusted Cox regression. The hazard ratios generated were 1.061 and 1.075 for progression free survival and overall survival, respectively; no confidence intervals were estimated by the company. The company also provided the results of indirect comparisons using naïve comparisons

(HR 1.190 and 0.959 for PFS and OS, respectively), and the matching adjusted indirect comparison method (HR 1.108 and 1.413 for PFS and OS, respectively, which unlike the other methods adjusted for baseline differences across treatment groups.

1.3. Summary of submitted cost effectiveness evidence

The cost-effectiveness systematic review of the literature undertaken by Novartis identified 14 studies. The quality assessment was carried out for only six studies out of 14. They compared effectiveness and cost-effectiveness of various treatment options for relapsed or relapsed and refractory multiple myeloma. The modelling approaches of these studies informed the structure of their model.

Novartis developed two cost-utility models as decision analytic semi-Markov model. The structure of the model for the economic analysis of the full PANORAMA-1 trial population (i.e. people who have received at least one prior therapy) includes two pre-progression health states, two post-progression health states and the death health state.
The model for the economic analysis of the subgroup of people who have received at least two prior therapies including IMiD and BTZ regimen includes two pre-progression health states, one post-progression health state and the death health state.

Both models are reported to capture the three key aspects of multiple myeloma that are affected by disease progression and the effects of treatment, namely survival, health related quality of life and costs.

Novartis model produced an ICER for PANO/BTZ/DEX triplet compared to BTZ/DEX of £79,025 cost per QALY gained for the full trial sample analysis of people who have received at least one prior therapy. The probability of PANO/BTZ/DEX being cost-effective at the £30,000 threshold was 0%.

In the subgroup of those patients with ≥2 prior therapies, including IMiD and BTZ, the ICER of PANO/BTZ/DEX vs LEN/DEX was £[redacted] and £[redacted] per QALY gained for subcutaneous and intravenous BTZ administration, respectively

1.4. Commentary on the robustness of submitted evidence

1.4.1. Strengths

- The economic models comparing PANO/BTZ/DEX with BTZ/DEX, in the full trial population, and PANO/BTZ/DEX with LEN/DEX in subgroup of people who had at least 2 prior lines for treatment including an IMiD and a BTZ based regimen analysis are structured around a set of health states

- which have been used in previous models submitted to NICE in this disease area (TA171 and TA338).[12]

- The economic model for the population of patients who have received at least one prior therapy draws primarily on a key clinical trial, PANORAMA-1, thus basing the analysis on a comparable set of data for both treatment arms being compared.

- In this model, an attempt has been made to account for some of the differences between the treatment protocol adopted in PANORAMA-1 and UK clinical practice for the BTZ regimen (i.e. stopping rules at cycle 4 and cycle 8).

- It is likely that the cost-effectiveness systematic review of the literature undertaken by Novartis contains all relevant studies. The systematic review identified 14 studies. The quality assessment was carried out for only six studies out of 14. These studies compared effectiveness and cost-effectiveness of various treatment options for relapsed or relapsed and refractory multiple myeloma.

1.4.2. Weaknesses

- In the economic model for the population of patients who have received at least one prior therapy The modelled survival functions may result in the survival benefits of PANO/BTZ/DEX relative to BTZ/DEX being overestimated;

- The utility scores used in this model may not account adequately for the relatively poorer safety profile in PANO/BTZ/DEX patients which was observed in the PANORAMA-1 trial;

The main weaknesses of the cost-effectiveness analysis between PANO/BTZ/DEX and LEN/DEX is the indirect comparison method used for the estimation of the hazard ratios for progression free survival and overall survival between LEN/DEX and PANO/BTZ/DEX. The Unadjusted Cox method was chosen to estimate the relative effectiveness between those two treatments. For this reason, the ERG lack confidence in the final ICER presented.

1.5. Key issues

1.5.1. Full trial sample analysis: people who have received at least one prior therapy

[1] National Institute for Health and Care Excellence. Technology Appraisal 338: Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib. March 2015. Available from: https://www.nice.org.uk/TA338.

[2] National Institute for Health and Care Excellence. Technology Appraisal 171: Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. June 2009. Available from: http://www.nice.org.uk/TA171.

- There is a divergence between the survival functions derived from the economic model and the Kaplan-Meier estimates in the original efficacy trial data (PANORAMA-1), with the modelled estimates exceeding the observed survival data in the PANO/BTZ/DEX group but being lower than the observed data in the BTZ/DEX group; this suggests that the modelled survival estimates may have exaggerated the benefits of PANO/BTZ/DEX.

- Whereas the analysis includes costs associated with individual AEs, the utility calculations do not make an adjustment for utility decrements associated with AEs; neither was a search conducted for evidence on AEs which might not be identified within the trial setting.

- Although the model estimated higher average utilities for the PANO/BTZ/DEX group, mapped from quality of life data collected as part of the trial, the ability of the quality of life assessments to capture the impact of adverse events is questionable; this is important given the emphasis placed on the poorer safety profile associated with the PANO/BTZ/DEX arm of PANORAMA-1 in the evidence submitted by the company. The QALY gains associated with PANO/BTZ/DEX may therefore have been overestimated.

- Given that the results of the model are relatively invariant to changes in time horizon, and given the concerns about the modelled survival estimates, a scenario analysis based on observed within-trial data would have been useful.

1.5.2. Subgroup analysis: people who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen

- While LEN/DEX is a relevant comparator for PANO/BTZ/DEX in patients who have received two or three prior lines of therapy including an IMiD and BTZ, the subgroup analysis does not explain why BTZ/DEX is not considered as a comparator in this subgroup. Thus, it is not possible to compare the cost-effectiveness of PANO/BTZ/DEX and BTZ/DEX in this subgroup. The interpretation of the cost-effectiveness results should take account of the absence of BTZ/DEX as a comparator in the analysis of the subgroup defined by at least 2 prior lines of treatment including an IMiD and BTZ based regimen.

- The indirect treatment comparison method by which the hazard ratios for progression free survival and overall survival between LEN/DEX and PANO/BTZ/DEX was estimated lacks robustness. Indeed, the Unadjusted Cox regression used to estimate the hazard ratios for the subgroups who received 2 to 3 prior lines of therapy from the PANORAMA-1 trial generated Kaplan-Meier curves for the two arms which were not parallel. Therefore this method is not valid in this application as the Kaplan-Meier curves do not satisfy the key assumption of proportional hazards.

- Effectiveness data (i.e. hazard ratios for LEN/DEX vs. PANO/BTZ/DEX) is taken from PANORAMA-1 for the subpopulation who have received at least two prior lines of therapy. In contrast, the cost-effectiveness analysis is intended to relate to a subset of this group, that is, those who received two

to three prior lines of therapy including an **IMiD and BTZ.** It is unclear therefore whether the effectiveness data included in the subgroup analysis are appropriate for the patient group of interest.

- The small difference in QALYs between the two therapies suggests that it is difficult to establish a statistical difference in effectiveness between PANO/BTZ/DEX and LEN/DEX in this subpopulation and makes the incremental analysis results very volatile.

1.6. Preferred ICER according to the ERG

For the ERG, the most plausible ICER is when the MAIC method is used as indirect comparison in order to estimate the hazard ratios for progression free survival and overall survival for the group of patients had at least 2 prior lines of therapy including an IMiD and BTZ and accounts for the correction of the frequency of specialist visits and the cost of Lymphopenia with BTZ administered subcutaneously. This ICER is £[redacted] per QALY gained for PANO/BTZ/DEX vs. LEN/DEX.

2. Background

2.1. Critique of company's description of underlying health problem

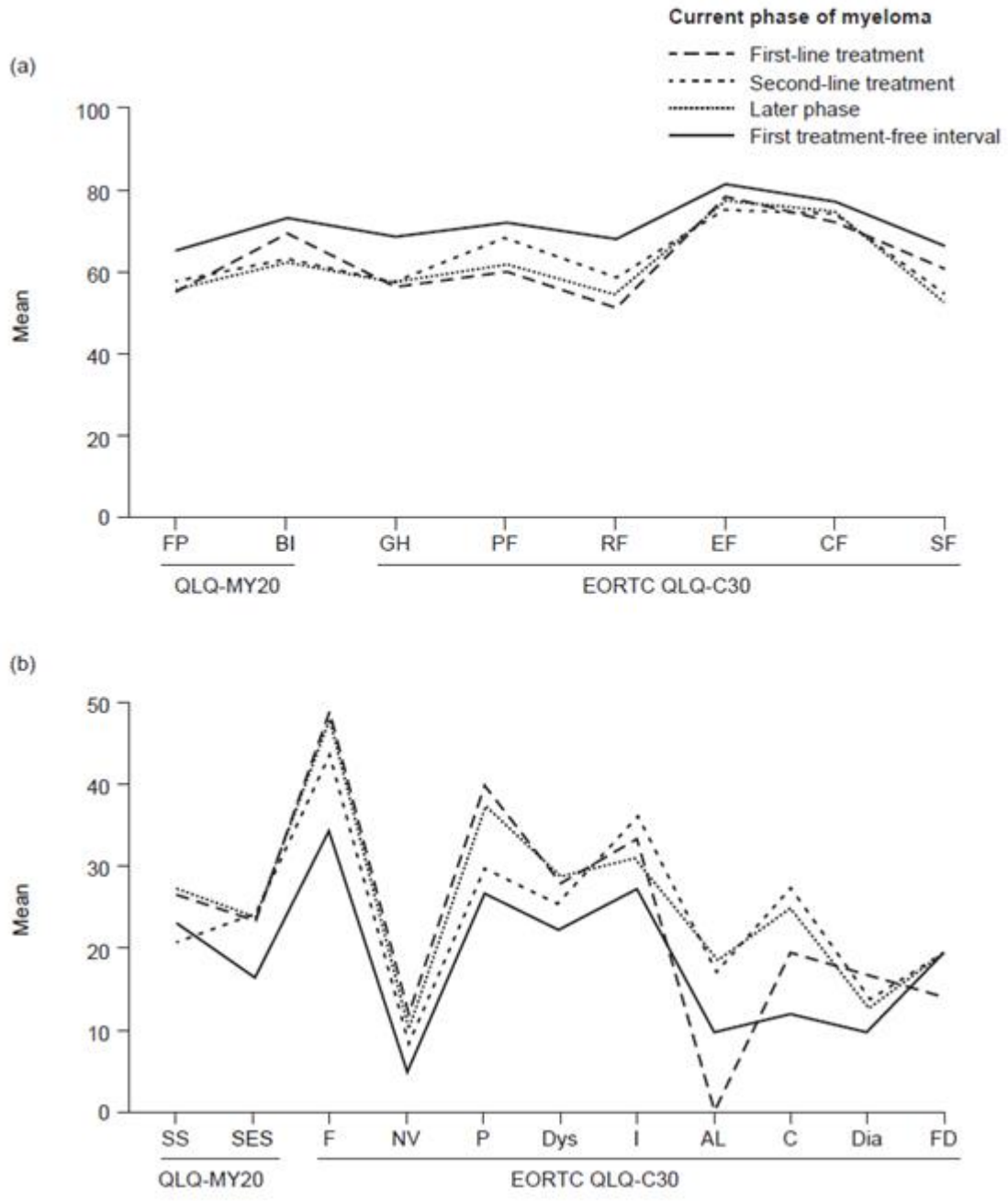
Note: The specific sections/pages of the submission referred by the ERG in this report apply to v0.2 of the submission.

Generally, evidence on clinical outcomes is distributed at various points throughout the document making it difficult to form a rounded picture of the effectiveness if treatment. Trial data on progression free survival, adverse events (AEs) and quality of life (QoL) all appear at different places in the report. Mean as well as median progression free survival (PFS)/overall survival (OS) would be particularly useful to report.

In Sections 3.1 to 3.2 of their submission, Novartis describe the underlying health problem. They provide a summary of the characteristics and progression of multiple myeloma (MM) and aetiology of the condition. It stated that most of the patients respond to first-line therapies and the majority relapse and/or become refractory to treatment and require further lines of therapy. As MM advances the symptom severity increases and health related quality of life (HRQL) declines. "*Patients with newly diagnosed MM have lower EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-core 30) scores, specifically the Global Health Status (GHS), Physical Functioning (PF) and Role Functioning (RF) scales, compared with those predicted for age-matched individuals from the general population".* In addition, it is stated that HRQL varies according to line of treatment. HRQL is higher during treatment-free interval (TFI). The company cite Acaster et al. 2013[3] UK survey data on HRQL and state that longer TFI is associated with improved HRQL (including physical functioning (PF), role functioning (RF) and 5-dimension EuroQol questionnaire (EQ-5D) score. The Figure 1 below presents mean values of for EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-core 30) and QLQ-MY20 (EORTC Quality of Life Questionnaire multiple myeloma module) from the Acaster study.

[3] Acaster S, Gaugris S, Velikova G, Yong K, Lloyd AJ. Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: a UK cross-sectional survey. Support Care Cancer 2013;21:599–607.

Figure 1: Mean values for EORTC QLQ-C30 and QLQ-MY20 a) functional domains and b) symptom scores according to stage of treatment in patients with MM



Source: Submission Figure 3

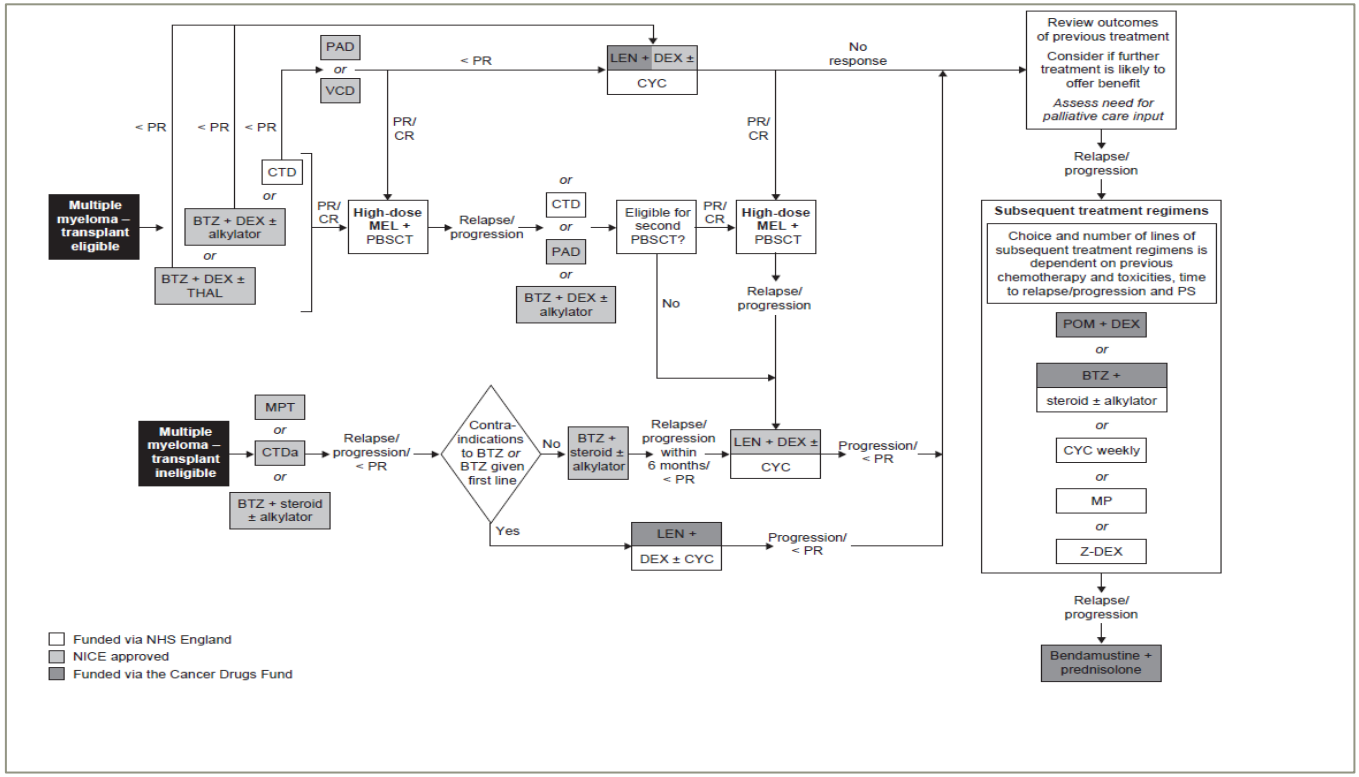
2.2. Critique of company's overview of current pathway of care and service provision

In Section 3.3 of their submission, Novartis outline that the management of rrMM should be individualised and treatment decisions should depend on timing of relapse, the efficacy and toxicity of drugs used in prior therapy, age, bone marrow and renal function, comorbidities and patient experience. As per findings of the STA (discussed in the subsequent sections) that panobinostat (PANO) extends TFI, the company link Acaster et al. paper findings (that the TFI is associated with higher HRQL) and claims that *"…provides patients with an extended period in remission together with an extended period without treatment and hence a better HRQL than that achieved with BTZ/DEX"* (page 40). HRQL was assessed during treatment until disease progression or discontinuation. Importantly, HRQL was not assessed during the TFI and Acaster et al. findings are used instead. These are discussed below.

The company cite the British Committee for Standards in Haematology (BCSH) guidelines and claim that the latter is in agreement with current National Institute for Health and Care Excellence (NICE) guidelines (page 37). However, subsequently, in Section 3.5 the submission claims that there is no overarching clinical guidance by NICE, but the guideline is due January 2016, and the submission cites a number of Technology Appraisals (TAs) providing recommendations for the management of MM or rrMM. The information on page 37 is, therefore misleading and should refer to NICE TAs that provide guidance on recommended lines of treatment.

In this section the company also present the draft National Chemotherapy Algorithm for the management of MM (NCAMM). The algorithm provides currently available and reimbursement treatment pathways. The algorithm is presented below.

Figure 2: Algorithm for the management of multiple myeloma in patients ineligible and eligible for ASCT



ASCT, autologous stem cell transplantation; BTZ, bortezomib; CR, complete response; CTD, cyclophosphamide, thalidomide and dexamethasone; CYC, cyclophosphamide; DEX, dexamethasone; LEN, lenalidomide; MEL, melphalan; MP, melphalan and prednisone; MPT, melphalan, prednisolone and thalidomide; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PAD, bortezomib, doxorubicin and dexamethasone; PBSCT, Peripheral blood stem cell transplantation; POM, pomalidomide; PR, partial response; PS, performance status; THAL, thalidomide; VCD, bortezomib, cyclophosphamide and dexamethasone; Z-DEX, oral idarubicin and dexamethasone.

National Chemotherapy Algorithms4

Source: Submission Figure 4

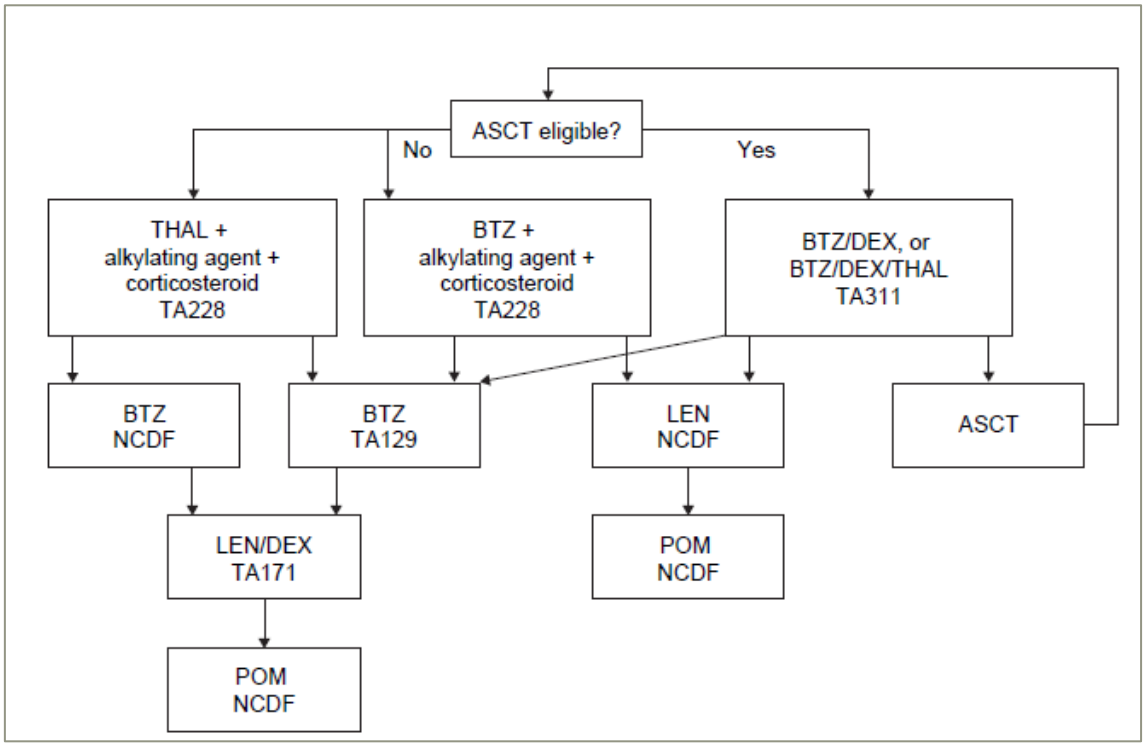
[4] National Chemotherapy Algorithms. Multiple myeloma. Available from: https://www.engage.england.nhs.uk/consultation/specialised-services-consultation/user_uploads/chemothrpy-algrthms-mltpl-myeloma.pdf (Accessed 8 May 2015).

The ERG sought clinical expert's view on the provided draft NCAMM algorithm. It was stated by our clinical expert that the NCAMM algorithm does not always represent current practice outside London. The algorithm is still in a draft status at this stage which might lead to think that there is no definite agreement on the appropriate clinical pathway in MM. Importantly, the draft NCAMM algorithm is based on median survival of 3.5 years however, median survival is currently is 6 to 7 years with some patients living even longer. If clinicians follow the pathway depicted in the NCAMM algorithm they might run out of treatment options quickly. Our clinical expert stated that if the patient had a good duration of response then it would make sense to repeat the same line of treatment another time rather than giving the next line of treatment as prescribed by the algorithm.

As noted above, the company also make a reference to BCSH guidelines. The clinical expert stated that BCSH guideline describes the treatment options available per line of treatment. The guideline, however, does not describe the sequence of treatments.

Alongside the draft NCAMM and BCSH recommendations, the company provide a treatment algorithm for the management of multiple myeloma in England and Wales based on NICE recommendations and National Cancer Drug Fund (NCDF) reimbursement approval. The algorithm outlines the treatment choices for patients who go through autologous stem cell transplantation (ASCT) or are ineligible for ASCT and TAs recommendations for 1^{st} – 4^{th} line of treatment. The algorithm is presented below.

Figure 3: Treatment algorithm for the management of multiple myeloma in England and Wales based on NICE recommendations and NCDF reimbursement approval



Note – NCDF funded options are only available in England.

ASCT, autologous stem cell transplantation; BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; NCDF, National Cancer Drugs Fund; NICE, National Institute for Health and Care Excellence; POM, pomalidomide; TA, technology appraisal; THAL, thalidomide.

Source: Submission Figure 5

The ERG sought expert opinion on treatment pathways depicted in the figure above. Namely, the ERG was unclear about the usage of BTZ funded by the NHS as per TA129 and at the same time by the NCDF in the 2nd line of treatment. The expert confirmed that TA129 NICE guidance is for single agent BTZ relapsed myeloma, however, in practice, BTZ is used in combination with DEX and cyclophosphamide (2nd line). Use of BTZ in combination with DEX/ cyclophosphamide, is however, under NCDF funding.

The expert confirmed that there was no overarching NICE guidance on management of multiple myeloma, but there were a number of TAs suggesting a number of treatment options. The expert stated that the algorithm for the management of multiple myeloma in England and Wales based on NICE recommendations and NCDF reimbursement approval (Figure 5 in the submission) represents the actual options of treating myeloma in practice.

In the treatment algorithm for the management of multiple myeloma in England and Wales based on NICE recommendations and NCDF reimbursement approval (Figure 5 of the submission), patients who

are eligible for ASCT will receive BTZ/DEX or BTZ/DEX/THAL induction as per TA311. The clinical expert stated that THAL induction is based on a trial, but in practice, most people will receive BTZ/DEX as induction treatment. This, however, contradicts the company's claim based on BCSH guidance that many UK patients receive THAL based therapy at induction (page 38).

Following the induction, patients who are eligible go through high dose chemotherapy (ASCT). Following the ASCT, patients who have a relapse of typically 18 months – 2 years can receive ASCT again. Patients who have a shorter remission or are no longer suitable for ASCT for any other reasons will receive LEN/DEX treatment, which is the relapse setting.

Moreover, the company note that usage of PANO along with bortezomib (BTZ) and dexamethasone (DEX) provides another treatment option for MM. The ERG sought the views of an expert on use of different medications on different lines. It was explained that if a patient had THAL at the 1st line and then relapsed, BTZ/DEX could be used in the 2nd line. The combination of PANO/BTZ/DEX could be then be used instead if superior to BTZ/DEX (as2nd line). If the patient had BTZ at induction, then LEN in the 2nd line can be used (NCDF funded). Following LEN therapy, BTZ can be used in the 3rd line. The combination of PANO/BTZ/DEX can then be used instead (as 3rd line). Our clinical expert explained that patients are not refractory forever and once the myeloma progresses, the clone responsible for the progression may be still sensitive to a line of treatment previously used, for example BTZ.

3. Critique of company's definition of decision problem

3.1. Population

The population defined in the NICE Scope[5] is people with multiple myeloma who have received at least 1 prior therapy. The population considered in the submission complies with the scope.

Novartis submitted an economic analyses of PANO for treating multiple myeloma in people who have received at least one prior line of therapy. In addition, Novartis submitted an economic analysis of the subgroup of patients with relapsed or relapsed and refractory MM who have received at least 2 prior lines of treatment including an IMiD and a BTZ based regimen. This analysis was presented in the Appendix 17 of the submission. The Committee for Medical Products for Human Use (CHMP) adopted a positive opinion recommending the granting of a marketing authorisation for PANO in combination with BTZ and DEX for treatment of relapsed and/or refractory multiple myeloma for the subgroup[6].

The PANORAMA-1 trial population included in the analysis were patients with relapsed or relapsed and refractory MM[7]. Table 6 on page 51 the number of received previous treatment regimens is 13. This number should be corrected to 1-3.

Because both terms were used in different occasion within the submission, the company was asked by the ERG to clarify whether the terms relapsed and refractory MM (rrMM) and MM in people who have received at least one prior therapy are being used interchangeably. The company stated that these terms were not fully interchangeable since relapsed is defined by disease that recurred in a patient that responded under a prior therapy, by reaching a MR or better, and had not progressed under this therapy. Relapsed and refractory, however, assumes at least two prior lines of treatment because patient are also refractory to another line. In the submission, the company refer in many instances to patients with rrMM when discussing the population of interest for this submission. For instance, in Section 3.4 page 41, the submission it is said states said that "*the therapeutic indication for panobinostat relates to the treatment of patients with rrMM"*. Another example is on Section 4.3.1 page 51: *"PANORAMA-1 trial, a phase 3, multicentre, randomised, double-blind, placebo-controlled study of*

[5] Referred to as "the scope" in the remainder of this report

[6] EMA. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003725/smops/Positive/human_smop_000846.jsp&mid=WC0b01ac058001d127 (Accessed 30/06/15)

[7] San-Miguel JF, Hungria VT, Yoon SS et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15:1195–206.

PANO/BTZ/DEX in patients with rrMM who have received between one and three prior treatment regimens". However, the following section 4.3.2 describes the inclusion criteria of the PANORAMA-1 trial as "*patients with relapsed or relapsed and refractory MM who had received one to three previous treatments".* Also in Section 5.1.1 on page 136 the company mention "*a systematic review was performed in August 2013 to identify economic evidence relating to second-line therapy of patients with rrMM"*. This occurs in several instances throughout the submission.

Therefore the ERG is generally concerned with the confusion that this creates for the PANO indication. The ERG believe that rrMM makes reference to the subgroup analysis of patients who had received at least 2 prior lines of treatment including an IMiD and a BTZ based regimen (the Appendix 17 of the submission).

Our clinical expert however, pointed to the fact that when clinicians talk of rrMM they typically mean relapsed, relapsed and refractory and primary refractory MM as defined in the paper published in Rajkumar et al.[8]

Novartis may also confuse the reader on page 11 of the Appendix 17 of the submission where they analyse the patients who had at least two prior lines of treatment including an IMiD and a BTZ based regimen which state that the "*economic analysis presented in this Appendix considers patients with relapsed or relapsed and refractory MM who had at least two prior lines of treatment including an IMiD and a bortezomib based regimen".*

The company also note that approximately 1300 patients in England and Wales would be eligible to receive PANO annually – a title of the of the paragraph 2 on page 41 , however, the source of the presented number is not presented and does not make any further reference to the cited number of 1300.

The company state that there is a lack of epidemiological data specific to patients with rrMM, but that figures are available for the number of people with MM. Based on CRUK figure, there were 4039 diagnoses in England in 2011 (4792 diagnoses in the UK). Again, it is not really clear why Novartis refer to rrMM population that is defined as the group that had two prior lines of treatment.

Novartis also stated that 37% of patients with MM in England survived cancer for 5 years or more[9]. However, the ERG found more up-to-date figures. Net 5 year survival in England and Wales was 47%[10].

[8] Rajkumar SV, Harousseau JL, Durie B et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Blood 2015:117;15:4691-5.

[9] Cancer Research UK. Myeloma survival statistics. Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/myeloma/survival/ (Accessed 17 June 2014).

[10] Cancer Research UK. Myeloma survival statistics. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/survival#heading-Zero (Accessed 9 July 2015).

The company cite "*5 year or more survival*" in England in the period of 2005-09 that is 37% from the Cancer Research UK website (CRUK). However, the origin of this number is slightly unclear. On the CRUK website the net survival for adults between 2005 and 2006 was 35.9% and in years 2010-11 5 year net survival was 47%. We were not able to find the source of the 37% figure cited by the company.

On page 41, paragraph 2 the submission states that there were 4792 diagnoses of MM in the UK in 2011 of which 4039 was in England. The numbers are confirmed on the CRUCK website [Accessed 30/06/15]. However, at the end of the same paragraph, the company note that there are 3117 patients with MM in England and Wales of whom 2194 received 1st line treatment and 86% receives 2nd line treatment with use of BTZ in around 71% of cases (we assume the figure comes from haematological Malignancy Research Network[11]).

3.2. Intervention

The intervention defined in the scope is treatment with PANO in combination with BTZ and DEX. The Section 2 of the submission described the technology assessed. The company was expecting an opinion from the CHMP in May/June 2015 and the European Medicines Agency (EMA) approval in August 2015. The company was asked to clarify whether they have received any of these since the submission of the STA to NICE. In their clarification they stated that the following CHMP opinion was expected to become published on 26th June 2015: "*Farydak, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent".*

The CHMP adopted a positive opinion recommending the granting of a marketing authorisation for PANO. The opinion was published on 26th June 2015. On the EMA website the indication for PANO is slightly different from what the company was expecting and is referring to relapsed and/or refractory multiple myeloma rather than multiple myeloma and states the following: "*Farydak, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with relapsed and/or refractory multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent*"[12]. Novartis state that PANO, in combination with BTZ and DEX, received regulatory approval from the US Food and Drug Administration (FDA) in 2014 for treatment of multiple myeloma in patients who received at least two prior regimens, including BTZ and an IMiD.

In Section 2.2 the company state that PANO in combination with BTZ and DEX is intended for patients with at least one prior therapy. The company also state that they present a subgroup analysis if the licence is more restricted and they refer to Appendix 4. However, no information is presented in

[11] Haematological Malignancy Research Network. Clinical management and outcome of myeloma. Version 3.0.

[12] EMA. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003725/smops/Positive/human_smop_000846.jsp&mid=WC0b01ac058001d127 (Accessed 30/06/15)

Appendix 4. It is only presented as a title: *"Appendix 4: Subgroup analysis (section 4.8)"*. It would have been better if the company referred to a specific section where they really present the analysis rather than to an appendix with no data.

In Section 2.3 the company present details of the treatment with PANO.

In Section 2.4 the company state that no specific infrastructure will be required for administration and management of PANO and PANO will be administrated in regiment along with BTZ and DEX. The ERG clinical expert confirmed that since PANO is an oral medication there is probably no additional resources that are needed for administration.

In the same section it is stated that monitoring will include:

- Laboratory tests;
- Bone marrow biopsy and aspirate; and
- Periodic skeletal survey (bone X-ray).

The company then refer to Section 5.5 for the details of resource use in the model. The Table 56 presents the monitoring scheme for pre-progression therapy and in contrast to Section 2.3 the monitoring scheme for pre-progression therapy includes:

- Serum protein assessment;
- Skeletal survey;
- Lab analysis (haematology, thyroid function test, blood chemistry); and
- Specialist visit.

This list, however, does not include bone marrow biopsy and aspirate as mentioned in Section 2.4 of the submission. The clinical expert confirmed 'patients with MM do not always undergo repeat marrow examination.

3.3. Comparators

The comparators defined in the scope are specified as follows:

- After 1 prior therapy: a) the use of BTZ and b) BTZ plus DEX;
- After 2 prior therapies: a) BTZ plus DEX, b) LEN plus DEX, and c) combination chemotherapy regimens with mephalan and doxorubicin, THAL and corticosteroids.

In the company submission the following was assessed:

- After 1 prior therapy: BTZ plus DEX; BTZ monotherapy was not assessed. Furthermore, expert opinion suggests that the use of BTZ in combination with DEX represents current practice in the UK.
- After 2 prior therapies: LEN plus DEX.

The company justify the exclusion of other therapies due to their lacking robust data and being of limited relevance to current clinical practice in England and Wales. In Table 1, under column rationale if different from the final NICE scope the company also stated "*bortezomib in combination with dexamethasone is not available in the UK after prior bortezomib"*. The latter statement does not explain the exclusion/inclusion rationale and the ERG see no relation of this statement to exclusion of the comparators in the scope.

Furthermore, the company present an analysis comparing PANO/BTZ/DEX to LEN/DEX for treating MM in people who have received at least two prior therapies including IMiD and BTZ regimens. This subgroup analysis was presented in the Appendix 17 of the submission. The ERG assessment for this subgroup is presented in Section 6 of this report.

3.4. Outcomes

The outcomes considered in the submission include:

- Progression free survival (PFS);
- Overall survival (OS);
- Response rates – CR/PR/nCR;
- Treatment free interval (TFI);
- AEs of treatment;
- HRQL.

This departs from the outcome measures considered in the scope, which included time to next treatment as an outcome. The company give a description of TFI and states that "*Treatment-free interval, the time period between discontinuation of panobinostat/bortezomib/dexamethasone or the comparator bortezomib/dexamethasone and resuming therapy with the next line of therapy on disease progression provides an addition and highly relevant measure of the benefit of therapy to patients. During this period patients experience a better quality of life being off treatment and without progressive disease*". However, this statement does not explain the rationale for not including time to next treatment.

3.5. Time frame

The time horizon for the economic analysis was 25 years. The proportion of patients alive at this point was about 0.03%.

4. Clinical effectiveness

4.1. Critique of company's approach

In this chapter we assess the clinical evidence provided by Novartis in their submission.

We start with a description and critique of Novartis's literature search strategy, followed by a description of the main studies selected for clinical effectiveness and their quality assessment.

We then look at the company's selection of outcomes and the statistical approach they used. This is followed by a summary of their submitted evidence for clinical effectiveness and our commentary on their validity.

4.1.1. Description of company's search strategy and comment on whether the search strategy was appropriate

4.1.1.1. Clinical Effectiveness Searches

The company presented a literature search protocol to support its review of clinical effectiveness. This protocol included systematic searches of key biomedical databases using a literature search strategy and hand searching of conference abstracts. The literature searching was last updated in December 2014.

The bibliographic searching used a search strategy that took the following form:

1. (terms for myeloma) AND
2. (terms for relapse or indicative terms for failure at first line) AND
3. (terms for thalidomide or bortezomib or lenalidomide or pomalidomide or carfilzomib or ixazomib or panobinostat)

A limit to phase 2, phase 3, and phase 4 trials, and a limitation to randomised controlled trials, was used. A limit to studies published in English language was applied and the searches were date limited 2003-December 2014.

The search strategy was applied in the following bibliographic databases: MEDLINE (OVID) and EMBASE (OVID). A simplified search strategy, consisting of database indexing terms for multiple myeloma and free text terms for relapsed or refractory, was used in The Cochrane Library (CENTRAL, NHS EEDS, DARE, CDSR and the HTA Library) in the first instance, and this was later supplemented with a search using controlled indexing terms for multiple myeloma.

The following conference proceedings were searched 2011-May 2013: ASH, ASCO, EHA, ESMO, IMF, IMW, ISPOR and AMCP. ASH, ASCO, EHA, ESMO, IMF, IMW were searched again 2013 - May 2014.

The brand name Farydak (sometimes spelt Faridak) was omitted in the company literature searches. The ERG clarified the rationale for this omission and the company replied that the omission has not impacted on the identification of relevant studies. The ERG ran scoping searches to test this point and reached a similar conclusion.

Within the submission, the company observe the paucity of mature trial data and, we note, is aware of further data that is now available to them. In view of additional data being available, and in reference to the submitted literature searches being over six months out of date, the ERG asked the company to update their literature searches. The company declined to do so.

In principal, the search syntax and search protocol was adequate to meet the requirements of this submission. We note, however, that the literature searches are now seven months old.

4.1.1.2. Indirect and mixed treatment comparisons

Separate searches for indirect and/or mixed treatment comparators were not undertaken for this submission. The ERG notes however that the range of comparators used in the literature searching is broader than required in the scope.

4.1.1.3. AEs

Separate searches for AEs were not undertaken for this submission. The ERG clarified the rationale for this decision and the company responded that they were aware of all the AE data for PANO.

Given the noted AE profile, the ERG would still have preferred that separate searches were conducted to look beyond one study which has driven this submission.

4.1.1.4. HRQL

Systematic searches were undertaken to identify utility and health related quality of life data. In total, two searches were made.

Search one (2003-2013) took the following form:

1. (terms for myeloma) AND
2. (terms for QLQ-C30, EQ-5D, time trade off etc.,)

Search two (2013-2014) took the following form:

1. (terms for myeloma) AND
2. (terms for QLQ-C30, EQ-5D, time trade off etc.,)
3. (terms for thalidomide or bortezomib or lenalidomide or pomalidomide or carfilzomib or ixazomib or panobinostat)

Literature searches were carried out in MEDLINE, MEDLINE in Process and EMBASE all via OVID. The searches were limited to human-only populations and to studies published in English.

The ERG is content with the searches for this element of the submission.

- Additional work undertaken by the ERG
  - Searches were undertaken in trials registries to identify any additional trials;
  - Scoping searches were undertaken to explore the omission of the brand name 'Farydak' from the efficacy searches.

4.1.2. Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate

In their review of clinical effectiveness of PANO, Novartis applied the inclusion/exclusion criteria listed in Table 1.

Table 1. Eligibility criteria used of study selection – June 2013 review

Clinical effectiveness	*Inclusion criteria*	*Exclusion criteria*
Populations	*Relapsed/refractory MM*	*Nonrelapsed/nonrefractory MM*
Interventions	*Bortezomib* *Carfilzomib* *Lenalidomide* *Panobinostat* *Pomalidomide* *Thalidomide* *Ixazomib*	*1) Induction or maintenance therapy or other combinations of therapy, i.e. results were reported for a sequence of therapy rather than a single regimen* *2) Treatment of interest is the focus of the study, i.e. studies of the treatment of interest in conjunction with a new treatment are not included*
Outcomes	*Response rate: CR and CR+VGPR+PR* *TTP* *OS*	*Analysis of prognostic factors*
Study design	*Clinical trials or RCT* *Phase II clinical trial* *Phase III clinical trial* *Phase IV clinical trial*	*1) Phase I/II studies unless they specifically reported results for phase II of the study* *2) Retrospective studies*
Publication type	*Report of primary data*	*Review, editorial, letter, or secondary*

Clinical effectiveness	Inclusion criteria	Exclusion criteria
		publication
Language restrictions	English	Non-English languages

Source: Submission Section 8.2. Appendix 2, page 9 (table not numbered)

The ERG noticed that PFS was not included in the initial search (as noted from Table 2). The company do not provide a rationale why PFS was omitted from the initial search. PFS is included in the update searches.

As noted above, the searches were updated in April and December 2014. The eligibility criteria is presented in the table below.

Table 2: Eligibility criteria used of study selection – April and December 2014 review

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Patients with relapsed/refractory multiple myeloma	Non-relapsed/non-refractory multiple myeloma Animal/ in vitro studies
Interventions	Panobinostat/ LBH-589 Thalidomide/ K-17 Bortezomib/ MG-341/ PS-341 Lenalidomide/ CC-5013 Pomalidomide/ CC-5013 Carfilzomib/ PR-171 Ixazomib/ MLN-9708 Elotuzumab/ HuLuc63 Vorinostat/ Zolinza Daratumumab/ HuMax-CD38 Dexamethasone*	Induction or maintenance therapy or other combinations of therapy, i.e. results were reported for a sequence of therapy rather than a single regimen Treatment of interest is the focus of the study, i.e. studies of the treatment of interest in conjunction with a new treatment are not included
Study design	Single- or double-blinded RCTs Non-RCTs Phase II clinical trial Phase III clinical trial Phase IV clinical trial Long term follow-up studies (e.g. open label studies)	Pharma-sponsored database analyses (except if conducted by Novartis) Pre-clinical and phase I studies Prognostic studies Case reports Editorials, commentaries and letters General reviews

Clinical effectiveness	Inclusion criteria	Exclusion criteria
		Systematic reviews and meta-analyses *Pharmacodynamic studies* *Retrospective studies*
Outcomes	*Response rate: CR and CR+VGPR+PR* *TTP/PFS* *OS*	*No relevant data on outcomes of interest* *Analysis of prognostic factors*
Publication	*English language* *Published from January 2013 to April 2014*	*Non-English language* *Published pre-2013* *Editorial* *Review* *Letter* *Reference included in original systematic review*

* Dexamethasone to be captured only when used in combination with an intervention named above
CR, complete response; OS, overall survival; PR, partial response; RCT, randomized controlled trial; TTP, time to progression; VGPR, very good partial response.

Source: Submission Section 8.2. Appendix 2, page 10 (table not numbered)

The inclusion criteria reflects the final scope issued by NICE; that is to include studies of patients who have received at least 1 prior therapy that is relapsed or refractory.

Overall these criteria seem appropriate to identify all relevant evidence on the clinical effectiveness of PANO. Despite this, the ERG requested clarification on some aspects of the search.

The submission includes flow diagrams that show the number of studies identified through the database searches and the number of studies included and excluded at each stage of the review and the reasons for exclusion. After the ERG requested clarification, the number of excluded studies in the first systematic review that took place in June 2013 was corrected from 87 to 386.

Only one study was identified for direct comparison.

In addition, indirect and mixed comparisons were conducted. These are discussed in Section 4.3.

4.1.3. Studies included and excluded

4.1.3.1. PANORAMA-1

The search strategy identified 3 references in the final search: 1 full paper and 2 abstracts. Only the full paper (PANORAMA -1) was deemed appropriate for the company for inclusion. The company do not give any more details on the 2 abstracts. No details of excluded papers are presented.

Table 3. List of relevant primary publications

Author, year (reference)	Trial number (acronym)	Intervention	Comparator	Population	Publication type
San-Miguel et al. 2014[13]; A correction to the original paper published as Lancet Oncol 2015;16:e6[14]	*PANORAMA-1 NCT01023308*	*PANO/BTZ/DEX*	*Placebo (PBO)/BTZ/DEX*	*Patients with rrMM who have received 1-3 previous treatment regimens*	*Full paper*

Source: Adapted from the submission Table 6

PANORAMA-1 is a multicentre RCT phase 3 trial. The summary of the trial is presented below.

Table 4: Summary of the methodology for PANORAMA-1 study

Study details	*PANORAMA-1*
Location	*215 centres in 34 countries*
Design	*Phase 3, multicentre, multinational, randomised, double-blind, placebo-controlled, parallel-group study, divided into two phases:* *a) treatment phase 1: 24 weeks (8 cycles of 21 days' duration each)* *b) treatment phase 2: 24 weeks (4 cycles of 42 days' duration each)*

[13] San-Miguel JF, Hungria VT, Yoon SS et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15:1195–206.

[14] San-Miguel JF, Hungria VT, Yoon SS et al. Correction to Lancet Oncol 2014; 15: 1195–206. Lancet Oncol 2015;16:e6.

Study details	*PANORAMA-1*
Eligibility criteria	***Inclusion criteria*** *Aged 18 years and older* *Measurable relapsed or relapsed and refractory MM* *1 to 3 previous treatments* *Eastern Cooperative Oncology Group performance status of ≤ 2* *ANC ≥ 1.5 × 10^9 cells/L* *Platelet count ≥ 100 × 10^9 cells/L* *Serum creatinine ≤ 1.5 × ULN* *Creatinine clearance ≥ 60 mL/min* *Normal electrolytes ≤ 1.5 × ULN* *Normal liver function ≤ 1.5 × ULN* ***Exclusion criteria*** *Primary refractory or BTZ-refractory MM* *Received previous treatment with a deacetylase inhibitor* *Received previous anti-myeloma treatment within 3 weeks before the start of the study* *Received experimental treatment or biological immunotherapy (including monoclonal antibodies) within 4 weeks before the start of the study* *Received previous radiation therapy within 4 weeks before the start of the study* *Needing valproic acid for any medical condition during the study or within 5 days prior to panobinostat /study treatment* *PN ≥ grade 2* *Impaired cardiac function (QTcF > 450ms) or gastrointestinal function* *Any other clinically significant heart disease or vascular disease* *Allogeneic stem cell transplant recipient with GVHD (active or on immunosuppression)* *Intolerance to BTZ or DEX* *Secondary primary malignancy within < 3 years of first dose of study treatment* *Major surgery ≤ 2 weeks prior to starting study drug* *Evidence of mucosal or internal bleeding* *Unresolved diarrhoea ≥ CTCAE grade 2* *History of HIV seropositivity* *Pregnancy or breast feeding*
Settings and locations where the data were collected	*215 centres in 34 countries including the following sites in the UK:* *University College Hospital, London (n = 11)* *St Bartholomew's Hospital, London (n = 9)* *Kings College Hospital, London (n = 5)* *New Cross Hospital, Wolverhampton (n = 2)* *Christie Hospital, Manchester (n = 2)* *Aberdeen Royal Infirmary, Scotland (n = 1)*

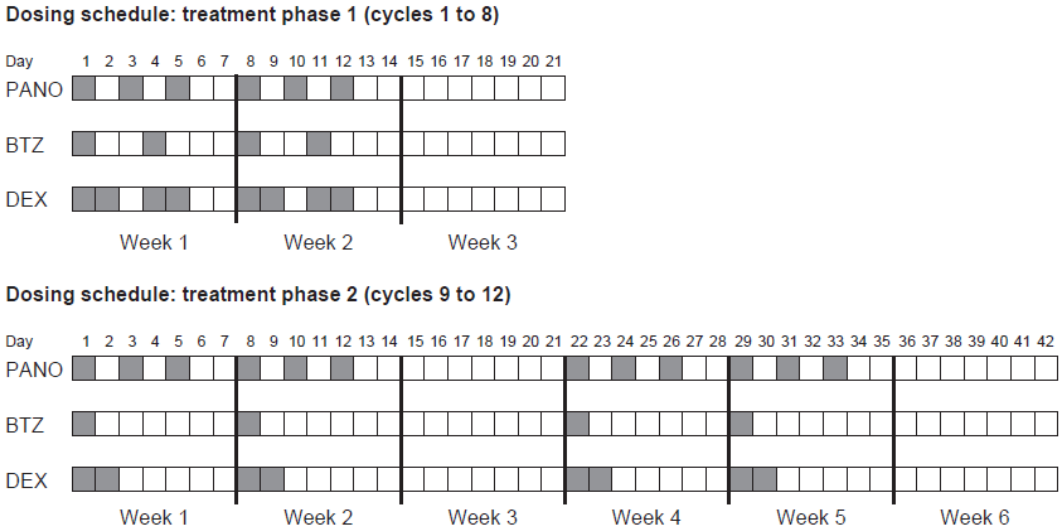
Study details	PANORAMA-1
Intervention(s) and comparator(s)	PANO/PBO (20 mg oral) three times a week, BTZ (1.3 mg/m^2 IV) twice a week, DEX (20 mg oral) four times a week, all administered at week 1 and week 2 followed by 1 week off treatment during phase 1. Treatment during phase 2 was identical with that during phase 1 except that BTZ was administered once a week Intervention, n = 387 Comparator, n = 381 Concomitant medications: prophylactic anti-emetics, growth factor support for anaemia and neutropenia if initiated before study entry; bisphosphonates if started before the start of screening; low molecular weight heparin or vitamin K inhibitors;
Primary outcomes (including scoring methods and timings of assessments)	PFS; response was assessed at 3-week intervals during treatment phases and at 6-week intervals thereafter according to modified EBMT criteria
Secondary outcomes (including scoring methods and timings of assessments)	OS ORR (CR, nCR and PR), MRR, TTR, TTP and DOR Safety (adverse events, ECG, laboratory parameters) HRQL (EORTC QLQ-C30 and QLQ-MY20, FACT/GOG-Ntx) PK of PANO and BTZ in a subset of Japanese patients Exploratory objectives: VGPR (IMWG 2008 criteria) and sCR
Pre-planned subgroups	Included: race, gender, age (< 65 versus ≥ 65 years; ISS stage (I versus II/III); renal impairment; number of prior lines of therapy (1 versus 2 or 3); prior use of BTZ; prior ASCT; prior use of IMiDs; prior use of BTZ; geographical region; MM characteristics (relapsed versus refractory/relapsed); cytogenetic risk (normal or poor)

Source: Submission Table 7

The maximum tolerable dose was found to be 20mg PANO three times a week and 1.3mg/m2 of BTZ.

The maximum duration of treatment was 12 cycles (or 16 3-weekly cycles) for both arms. The regimens consisted of two treatment phases as presented in Figure 4 below. In contrast to the eight 3-week cycle UK clinical practice, BTZ was administered up to cycle 16 (this is discussed further below). Additionally, there was no stopping rule at cycle 4 to test BTZ response.

Figure 4: Dosing schedule in treatment phases 1 and 2

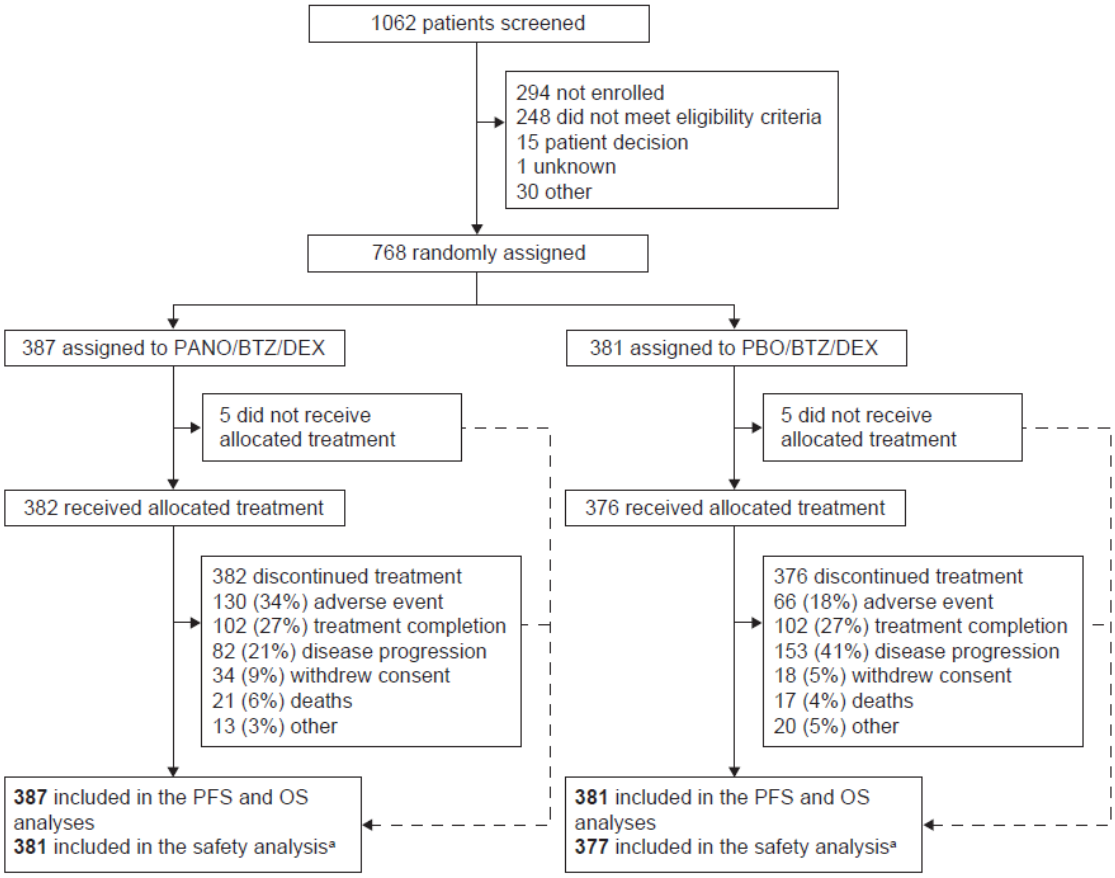


Source: Submission Figure 8

PANORAMA-1 trial was funded by Novartis.

In total 387 patients were included in PANO/BTZ/DEX group and 381 patient were in PBO/BTZ/DEX. The patient disposition is presented below.

Figure 5: Patient disposition in the PANORAMA-1 study



[a]One patient randomly assigned to receive panobinostat was given placebo during cycles 1 and 2 because of a misallocation error; the patient was subsequently given panobinostat from cycle 3 until discontinuation of treatment, but was included in the placebo group for safety analysis

Source: Submission Figure 10

Table 10 of the submission presents the characteristics of the PANORAMA-1 tail. The table is replicated below.

Table 5: Patient characteristics of PANORAMA-1 trial

Characteristic	*PANORAMA-1 (n = 768)*	
	PANO/BTZ/DEX (n = 387)	*PBO/BTZ/DEX (n = 381)*
Age, years		
Mean ± SD	*62.4 ± 9.34*	*61.8 ± 9.43*
Median age (range)	*63.0 (28 to 84)*	*63.0 (32 to 83)*
Age category, n (%)		

Characteristic	PANORAMA-1 (n = 768)	
	PANO/BTZ/DEX (n = 387)	PBO/BTZ/DEX (n = 381)
< 65 years	225 (58.1)	220 (57.7)
> 65 years	162 (41.9)	161 (42.3)
Male, n (%)	202 (52)	205 (54)
Time since diagnosis, months		
N	386	381
Mean ± SD	46.7 ± 38.02	49.0 ± 34.78
Median (range)	37.1 (2.4 to 308.1)	38.9 (2.4 to 300.2)
ECOG performance status, n (%)		
0	175 (45)	162 (43)
1	191 (49)	186 (49)
2	19 (5)	29 (8)
Creatinine clearance, n (%)		
60 to 89 mL/min	265 (68)	249 (65)
≥ 90 mL/min	120 (31)	129 (34)
Missing	2 (< 1)	3 (< 1)
ISS staging, n (%)		
Stage I	156 (40.3)	152 (39.9)
Stage II	104 (26.9)	92 (24.1)
Stage III	77 (19.9)	86 (22.6)
Not assessed	50 (12.9)	51 (13.4)
MM characteristics, n (%)		
Relapsed and refractory	134 (35)	141 (37)
Relapsed	247 (64)	235 (62)
Other	6 (2)	5 (1)
Prior autologous stem cell transplantation, n (%)	215 (56)	224 (59)
Previous treatment lines, n (%)[a]		
N	386	381
Mean ± SD	1.7 ± 0.76	1.7 ± 0.78
Median (range)	1.0 (1 to 4)	1.0 (1 to 3)
1	198 (51.2)	198 (52.0)
> 2	189 (48.8)	183 (48.0)
Prior therapy, n (%)		
BTZ	169 (43.7)	161 (42)
LEN	72 (18.6)	85 (22)
THAL	205 (53.0)	188 (49)
Melphalan	310 (80.1)	301 (79.0)
DEX	308 (80)	315 (83)
BTZ/IMiD	94 (24.3)	99 (26)
BTZ/DEX	147 (38.0)	143 (38)
BTZ/LEN	34 (8.8)	45 (11.8)

Characteristic	PANORAMA-1 (n = 768)	
	PANO/BTZ/DEX (n = 387)	PBO/BTZ/DEX (n = 381)
DOX	129 (33)	138 (36)
VIN	115 (30)	117 (31)
Cytogenetic risk group, n (%)[b]		
N	120	124
Normal risk	79 (65.8)	88 (71.0)
Poor risk	24 (20.0)	13 (10.5)
Unknown or missing	17 (14.2)	23 (18.5)

[a]One patient in the PANO/BTZ/DEX group had received no previous anti-neoplastic treatments and another had received more than three previous treatments.

[b]Based on number of patients who consented for biomarker protocol

Source: Submission Table 10

The presented number of the patients do not sum up in some tabs. The numbers were cross-checked with San-Miguel et al.[15] The ERG found despite San-Miguel et al. explanation on missing patients in ECOG status, a patient is still missing in PBO group. Time since diagnosis figures were not found in San-Miguel et al.

Additionally the number of patients who received more than two lines of therapy should be 188 as per San-Miguel et al. The company did not provide appendices for this paper.

4.1.3.2. Non-randomised and non-controlled evidence

Two published non-RCTs were presented to provide evidence for the efficacy and safety of PANO in combination with BTZ/DEX relative to BTZ/DEX. The summary of these studies are presented in Table 30 of the submission.

It is not clear to the ERG how these two studies have been identified by the company as they do not seem to be the result of the systematic review described in Section 4.1.2

The details of the two studies are reported in the Table 6 below.

[15] San-Miguel JF, Hungria VT, Yoon SS et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15:1195–206

Table 6 List of relevant non-randomised controlled trials of PANO in relapsed/refractory multiple myeloma

Trial number (acronym)	*Intervention*	*Population*	*Objectives*	*Primary study reference*	*Justification for inclusion*
DUS71 *PANORAMA-2* *NCT01083602* *Phase 2 multi-centre single-arm open-label study*	*PANO/BTZ/ DEX*	*Patients with relapsed and BTZ-refractory MM* *N = 55*	*To compare the efficacy and safety of PANO/BTZ/ DEX versus BTZ/DEX for treatment of rrMM* *Primary endpoint: ORR* *Secondary endpoints:* *MR, TTR, DoR, PFS, TTP, OS, safety and tolerability*	*Richardson et al. Blood 2013;122:2331–7*[16]	*Provides efficacy and safety data for PANO/ BTZ/DEX*
B2207 *Phase 1b study* *NCT00532389* *Phase 1b multicentre open-label post dose-escalation study*	*PANO/BTZ/ DEX*	*Patients with relapsed rrMM* *N = 62 (15 in dose expansion phase)*	*To determine the maximum tolerated dose of PANO in combination with BTZ/DEX and to evaluate safety, pharmacodynamics/pharmacokinetics, and efficacy* *Primary endpoint:* *Confirmation of MTD* *Secondary endpoints:* *Safety and tolerability, PK and PD of biomarkers, preliminary efficacy*	*San-Miguel et al. J Clin Oncol 2013;31:3696−703*[17]	*Provides efficacy and safety data for PANO/ BTZ/DEX*

BTZ, bortezomib; DEX, dexamethasone; DoR, duration of response; MM, multiple myeloma; MR, minimal response; MTD, maximum-tolerated dose; ORR, overall response rate; OS, overall survival; PANO, panobinostat; PD, pharmacodynamic; PFS, progression-free survival; PK, pharmacokinetics; rrMM, relapsed/refractory multiple myeloma; TTP, time to progression; TTR, time to response.

Source: Submission Table 30

[16] Richardson PG, Schlossman RL, Alsina M et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. Blood 2013;122:2331–7.

[17] San-Miguel JF, Richardson PG, Gunther A et al. Phase Ib study of panobinostat and bortezomib in relapsed or relapsed and refractory multiple myeloma. J Clin Oncol 2013;31:3696–703.

The phase 2 PANORAMA-2 is an open-label study that investigated the efficacy and safety of PANO/BTZ/DEX in patients with rrMM who are refractory to BTZ (patients refractory to BTZ were excluded in PANORAMA-1). The summary of the tumour responses is presented in Table 7 below.

Table 7: Tumour responses reported in the PANORAMA-2 study at the end of eight cycles

Best response at the end of eight cycles (confirmed at 6 weeks)	*Number of patients, n (%) n = 55*
Overall response	*19 (34.5)*
Complete response	*0 (0.0)*
Near-complete response	*1 (1.8)*
Partial response	*18 (32.7)*
Minimal response (MR)	*10 (18.2)*
Clinical benefit rate (≥ MR)	*29 (52.7)*
Stable disease	*20 (36.4)*
Progressive disease	*3 (5.5)*
Unknown[a]	*3 (5.5)*

[a] Patients without post-baseline assessment

Richardson et al.; 2013[18]

Source: Submission Table 32

The median PFS reported was 5.4 months overall. The median OS was not yet reached in the original publication. However, updated data presented in abstract form, reported a median OS of 17.5 months (95% CI, 10.8 to 25.2 months)[19].

The safety profile of PANORAMA-2 was also assessed. It was found that 87.3% of patients discontinued due to disease progression and 18.2% due to AEs. The summary of AEs is presented in Table 33 of the submission. The PANORAMA-2 data is not incorporated in the economic analysis.

Table 8 Haematological and non-haematological AEs regardless of study drug relationship occurring in the PANORAMA-2 study

Adverse events, %	*PANO/BTZ/DEX (n = 55)*
Non-haematological adverse events reported in > 5% of patients in treatment group: any grade/grade 3 or 4 (% patients)	
Diarrhoea	*71/20*
Fatigue	*69/20*
Nausea	*60/6*

[18] Richardson PG, Schlossman RL, Alsina M et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. Blood 2013;122:2331–7.

[19] Richardson PG, Schlossman RL, Alsina M et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. Blood 2013;122:2331–7.

Adverse events, %	*PANO/BTZ/DEX (n = 55)*
Hypokalaemia	*22/7*
Hypotension	*20/9*
Asthenia	*20/9*
Abdominal distention	*20/7*
Pneumonia	*16/15*
Dehydration	*16/5*
Abdominal pain	*16/6*
Flatulence	*11/6*
Sepsis	*9/9*
Syncope	*9/9*
Septic shock	*6/6*
Hypophosphatemia	*6/6*
Haematological adverse events reported in > 5% of patients in treatment group: any grade/grade 3 or 4 (% patients)	
Thrombocytopenia	*66/64*
Anaemia	*47/15*
Neutropenia	*18/15*

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.
Richardson et al. 2013[20]
Source: Submission Table 33

The second non-RCT study presented in the submission was a dose-escalation/safety single arm open label phase 1b trial[21]. The trial aimed to test the maximum tolerated dose of PANO and BTZ, evaluate safety, pharmacodynamics/pharmacokinetics and efficacy. The study found that maximum tolerated dose was 20mg of PANO three times a week and 1.3mg/m² of BTZ (based on 15 patients). Incidence of common grade 3 / 4 AEs was ≥15% with thrombocytopenia being the most prevalent (81%), followed by neutropenia (60%), asthenia (26%), anaemia (18%), leukopenia (18%) and diarrhoea (16%).

The ERG noted that the study paper San-Miguel et al. 2013 report AEs regardless of causality occurring ≥25% for grade 3 / 4 in Table 2 for thrombocytopenia (81%), neutropenia (60%), asthenia (26%), anaemia (18%) and diarrhoea (16%), whereas leukopenia (18%) is reported in Table A3 for AEs regardless of causality occurring ≥10%.

[20] Richardson PG, Schlossman RL, Alsina M et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. Blood 2013;122:2331–7.
[21] San-Miguel JF, Richardson PG, Gunther A et al. Phase Ib study of panobinostat and bortezomib in relapsed or relapsed and refractory multiple myeloma. J Clin Oncol 2013;31:3696–703.

4.1.3.3. Comparators

As noted above, one study was identified that directly compares PANO/BTZ/DEX with PBO/BTZ/DEX (PANORAMA-1).

4.1.4. Studies not included in the submission

The ERG consider that all studies relevant to the direct comparison of PANO/BTZ/DEX with BTZ/DEX were included in the submission.

4.1.5. Description and critique of company approach to validity assessment

In this section one study presented in Novartis submission is assessed for their validity. PANORAMA-1 was initially assessed by Novartis and is presented in Section 4.6 Table 11 and also is duplicated in the appendix 3. Table 9 provides the quality assessment of study PANORAMA-1.

Table 9: Critical appraisal of relevant RCTs

PANORAMA-1			
Novartis comments			***ERG comments***
Study question	***How is the question addressed in the study?***	***Grade (yes/no/not clear/N/A)***	
Was randomisation carried out appropriately?	*Patients were centrally assigned to each treatment arm via IXRS in a ratio of 1:1*	*Yes*	*This is appropriate*
Was the concealment of treatment allocation adequate?	*PANO and matching placebo were supplied as hard gelatine capsules. The identities of the treatments were concealed by the use of study drugs (PANO and placebo) that were identical in packaging, labelling, schedule of administration and appearance*	*Yes*	*This method is adequate*
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	*Treatment arms were well balanced with respect to baseline demographic characteristics*	*Yes*	*Patient characteristics presented on Table 10 of the submission show comparable study groups*
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of	*Patients, investigator staff, persons performing the assessments and data analysts remained blind to the identity of the treatment from the time of randomisation until final*	*Yes*	*According to San-Miguel et al. patients, physicians and the Novartis clinical trial team were masked to treatment allocation; the statisticians who did the analysis were masked to*

PANORAMA-1			
Novartis comments			**ERG comments**
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**	
these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	database lock		treatment allocation until unblinding at the time of the analysis of the primary endpoint
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No. Over the course of the study all patients in both groups discontinued treatment. However, the reasons for discontinuation differed between treatment groups. The most common reasons for treatment termination were adverse events (130 [34%] in the PANO group versus 66 [17%] in the placebo group) and disease progression (82 [21%] versus 153 [40%])	Yes	San-Miguel et al. present a trial profile in Figure 2. The most common reasons for treatment termination were adverse events. Serious adverse events were reported in 228 (60%) of 381 patients in PANO group and 157(42%) of 377 patients in the placebo group. Other reasons for discontinued treatment included disease progression, consent withdrawal, deaths or other (not specified)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The primary outcome, key secondary outcome and most other secondary outcomes listed in the CSR are reported in the primary manuscript	Yes	Interim analyses were scheduled to occur after 33% and 80% of the 460 progression-free survival events required for the final analysis were recorded. The planned second interim analysis was not done. The ERG asked Novartis to comment on this. The company said that the reasons were unknown to them and are seeking advice from the statisticians. It is also stated that results for health-related quality of life and the pharmacokinetics of PANO and BTZ in a subset of Japanese patients will be reported elsewhere
Did the analysis include an	Yes; the primary analysis was assessed in the full analysis set	Unclear	The primary endpoint was progression-free survival and was

PANORAMA-1			
Novartis comments			**ERG comments**
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**	
intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*which included all randomised patients*		*analysed by intention to treat*

Source: Submission Table 11

In addition, Novartis discuss the sample size calculations (Section 4.4.2). In order to calculate the sample size, assumptions were made on median PFS for both PANO/BTZ/DEX and control group. As noted above, the planned second interim analysis was not reported in San-Miguel at al. No explanation of reasons are presented.

There are, however, additional limitations to the study as identified by Novartis:

1. The use of BTZ is different from NICE TA129 recommendation. According to TA129, there is a stopping rule at cycle 4 to test the response of patients. If the response is not sufficient at cycle 4, the patients stop their treatment. In PANORAMA-1 however, patients continued treatment until cycle 12. Novartis have tried to implement this stopping rule in the model (as discussed below) however, the ERG is concerned with the impact that this may have on the cost-effectiveness;
2. In PANORAMA-1, BTZ was administrated intravenously. The NHS in England and Wales does still administer BTZ intravenously according to guidelines. However, in the UK practice it is increasingly administrated subcutaneously. It is said that subcutaneous administration is better tolerated. Section 4.13.2 in the submission discusses the safety. The safety section will be discussed further in Section **Error! Reference source not found.**;
3. The proportion of patients who received prior stem cell transplantation in PANORAMA-1 is higher than the 18% proportion documented for the UK[22]. In PANORAMA-1 215 out of 387 (56%) and 224 out of 381 (59%) have received transplantation in PANO/BTZ/DEX and PBO/BTZ/DEX groups respectively.

In addition, the population of PANORAMA-1 trial is younger than the UK MM patients, the median age in PANORAMA-1 was 63 years (for both arms; ranging between 28 to 84 for PANO group and 32-83 in the

[22] Haematological Malignancy Research Network. Clinical management and outcome of myeloma. Version 3.0.

control arm). The UK study found that 60% patients are diagnosed at age 70 or later with the median age at diagnosis being 73.1 years (range 33.4-95.5)[23].

HRQL was assessed during treatment until disease progression or discontinuation. Importantly, HRQL was not assessed during the TFI. The ERG is not clear on why this is the case. We discuss the use of alternative utilities later in the report along with methods and results of the economic evaluation (Section 5).

On page 59, the company state that the final PFS analysis is to be performed when approximately 460 events have been observed. The ERG has clarified with Novartis that this sentence was misleading and in fact final PFS analysis was performed at the first data cut off (September 2013) as stated on page 68 Section 4.7.2 since 467 PFS events were recorded at that time.

OS data has been reported for the 10 September 2013 cut-off and the 18 August 2014 cut-off. As clarified by the company the survival data from both analysis are not mature since only 359 (86.5%) of the target 415 OS events had occurred in August 2014. This is further discussed in Section 4.2.5Error! Reference source not found. below.

4.1.6. Description and critique of company's outcome selection

The outcome selection in Novartis's submission is a direct reflection of those included in PANORAMA-1.

Primary Efficacy Endpoint

Primary and secondary efficacy analyses were conducted on all patients on PANORAMA-1 trial.

The primary outcome of the study was:

- Progression free survival (PFS). PFS was assessed in the full analysis set. This was defined as the time from randomisation until:
  - Documented disease progression;
  - Relapse from complete response;
  - Or death, whichever came first[24].

Observations were censored at the date of last response assessment for subjects who either:

- Had not progressed or,
- Had a new treatment.

Secondary Efficacy Endpoint

[23] Haematological Malignancy Research Network. Clinical management and outcome of myeloma. Version 3.0

[24] San-Miguel JF, Hungria VT, Yoon SS et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15:1195–206.

Secondary outcomes analysed are:

- Overall survival – defined as he time from randomisation to death from any cause;
- Response rate – partial response or better, near complete or complete response, or minimal response;
- Response duration – defined from first occurrence of partial response or better;
- Time to progression – defined as time from randomisation to first documented disease progression or relapse;
- Safety.

Table 10: Primary and secondary outcomes for the PANORAMA-1 study

Trial	*Primary outcome(s) and measures*	*Reliability/validity/ current use in clinical practice*	*Secondary outcome(s) and measures*	*Reliability/current use in clinical practice*
PANORAMA-1	*The primary endpoint was PFS (as assessed by the investigators on the basis of the modified EBMT criteria), and was defined as the time from randomisation until documented disease progression, relapse from complete response, or death, whichever came first*	*PFS is a recognised outcome measure for assessment of treatments for MM.[252627] Unlike OS, it is not influenced by therapy following relapse and therefore can be a more accurate measure of treatment efficacy*	*Key secondary endpoint: OS* *Other secondary outcomes:* *ORR (CR, nCR and PR), MRR, TTR, DOR and TTP* *Safety (adverse events, ECG, laboratory parameters)* *HRQL (EORTC QLQ-C30 and QLQ-MY20, FACT/GOG-Ntx)* *Exploratory endpoints: VGPR (IMWG 2008 criteria) and sCR* *PK of PANO and BTZ in a subset of Japanese*	*OS is a well-recognised outcome measure for treatments of MM because therapies aim to prolong survival. ORR (CR, nCR and PR) are recognised measures of efficacy in MM as defined using the EBMT criteria.[2829]*

[25] lade J, Samson D, Reece D et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol 1998;102:1115–23.

[26] Richardson PG, Barlogie B, Berenson J et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003;348:2609–17.

[27] Durie BG, Harousseau JL, Miguel JS et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467–73.

[28] Richardson PG, Barlogie B, Berenson J et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003;348:2609–17.

[29] Durie BG, Harousseau JL, Miguel JS et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467–73.

Trial	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/current use in clinical practice
			patients	

Source: Submission Table 8

Response to therapy was assessed based on modified EBMT (mEBMT) criteria after 8 cycles of therapy (in contrast to 4 weeks of the UK practice). PFS was assessed at 3-week intervals during treatment phases and at 6-week intervals thereafter according to modified EBMT criteria.

4.1.7. Description and critique of the statistical approach used

The company say that statistical tests were performed on the main study efficacy outcomes and that statistical analysis was only performed on the key secondary endpoint OS if the primary endpoint was statistically significant. It is stated in the submission (page 60) that *"a two-sided log rank test with a cumulative type I error of α = 0.05 and a power of 1-β = 90% was used for the 3-look group sequential plan. Under the above assumptions and using a 1:1 randomisation to the two arms of this trial, a total of 460 PFS events were required."*

However, it should be noted that the company report p values only for the primary efficacy outcome PFS and the key secondary outcome OS. The OS data are not mature and the final analysis of OS is planned when 415 survival events have occurred.

4.1.8. Summary statement

Following responses to the ERG's questions for clarification in relation to the effectiveness searches, we are content that the searches presented in this submission are suitable for the task.

The ERG opinion is that the company's search strategy on clinical effectiveness was generally appropriate. However to note is that:

- The fact that no separate searches were undertaken for AEs is perceived as a weakness;
- Search of the outcome PFS was omitted from the initial search that took place in the June 2013 review however, PFS was included in the update search (December 2014);
- No information on excluded papers was presented;
- It is not clear to the ERG how the non-randomised trials were identified.

The methodology used to assess the quality of the included RCT was adequate.

The ERG consider that the evidence submitted generally reflects the decision problem outlined in the final scope of the submission.

One of the main commentary of the ERG is the use of terms relapsed and relapsed and refractory multiple myeloma. The ERG is generally concerned with the confusion that this creates for the PANO

indication. The ERG believe that rrMM makes reference to the subgroup population analysis of patients who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen.

Additionally, according to the final NICE scope, time to next treatment was one of the outcomes to be analysed. However, Novartis do not give a valid explanation why it was excluded.

The ERG is generally concerned with absence of stopping rule that is the UK practice at cycle 4. As noted before, this rule was not implemented in the PANORAMA-1 trial and patients continued treatment up to cycle 12. Moreover, as noted by the company "*there is a notable difference between the way bortezomib was administered in PANORAMA-1 compared with current UK practice"*. Patients do not continue BTZ treatment beyond cycle 8 in the UK. Although this was implemented in the modelling approach as the model allows for 10% of the population to continue treatment beyond cycle 8 (this is further discussed in Section5.1.2).

4.2. Summary of submitted evidence

The company present the analysis of the efficacy outcomes from PANORAMA-1 trial at the data cut-off of 10 September 2013 and OS data at the data cut-off of 18 August 2014. On page 135 they state that the further trial data would become available in May/June 2015.

The ERG sought clarification on information on final trial data. Novartis stated the final OS data is planned to be published in December at the 57th ASH Congress, should the required number of events happened in time for data submission.

4.2.1. Progression free survival

The company present the PFS results as the primary outcome from PANORAMA-1.

In Table 11 we report the results at the data cut-off of 10 September 2013 as per investigator assessment, as per independent review, as well as the multivariate Cox model analysis. As noted in section 4.1.5, the ERG has clarified that final PFS analysis was performed at the first data cut off (September 2013) since 467 PFS events were recorded at that time.

The ERG is not clear why the results for PFS are only reported for 381 patients instead of 387 for the treatment arm and 377 patients instead of 381 for the control arm.

It should be noted that the number of events observed by the investigator and the independent reviewer are different; the independent reviewer observed more PFS events and less patients censored in both arms. The median time to events are also different for the control arm: 8.08 and 8.31 months for the investigator and the independent reviewer respectively. However, the HR are similar with the same CI and p value: 0.63 (0.52 to 0.76), p value < 0.0001.

Table 11: Progression-free survival PANORAMA-1 study

		PANO/BTZ/DEX (n = 381)	*PBO/BTZ/DEX (n = 377)*
PFS by investigator	*PFS events, n (%)*	*207 (53.5)*	*260 (68.2)*
	Censored, n (%)[a]	*180 (46.5)*	*121 (31.8)*
	Median time to event, months[b] *(95% CI)*	*11.99 (10.32 to 12.94)*	*8.08 (7.56 to 9.23)*
	Hazard ratio (95% CI) p value	*0.63 (0.52 to 0.76) < 0.0001*	
PFS by independent review	*PFS events, n (%)*	*241 (62.3)*	*283 (74.3)*
	Censored, n (%)	*146 (37.7)*	*98 (25.7)*
	Median time to event, months[b] *(95% CI)*	*11.99 (10.51 to 13.50)*	*8.31 (7.62 to 9.92),*
	Hazard ratio (95% CI) p value	*0.63 (95% CI 0.52 to 0.76) < 0.0001*	
Stratified Cox model adjusting for baseline characteristics[c]	*PFS events, n*	*207*	*260*
	Censored, n	*180*	*121*
	Median time to event, months[b] *(95% CI)*	*11.99 (10.32 to 12.94)*	*8.08 (7.56 to 9.23)*
	Hazard ratio (95% CI) p value	*0.58 (0.48 to 0.71) < 0.0001*	

[a]In the PFS analysis according to investigator assessment, 180 (46.5%) of the patients in the panobinostat group were censored compared with 121 (31.9%) in the placebo group. The main causes of censoring were lack of efficacy (22.2% panobinostat; 14.2% placebo), consent withdrawal (19% panobinostat; 11.8% placebo), > 2 missing assessments prior to event (9.3% panobinostat; 7.3% placebo), ongoing, in follow-up (9% panobinostat; 3.9% placebo), and new cancer therapy added (5.9% panobinostat; 6.3% placebo).

[b]Kaplan–Meier estimates.

[c]Baseline covariates included in the Cox proportional hazard model are: treatment group; age group; renal impairment; prior stem cell transplantation; clinical staging according to International Staging System, sex; race and geographic location; prior use of IMiDs; prior use of bortezomib (yes versus no); and number of prior therapies (1 versus 2/3).

Hazard ratio and 95% CI of PANO/BTZ/DEX versus PBO/BTZ/DEX are obtained from a stratified Cox model. The two-sided p value is obtained from the stratified log-rank test. p values for analyses other than the primary analysis are presented for descriptive purposes and for an assessment of the consistency and robustness of the primary analysis in terms of statistical significance.

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; IMiD, immunomodulatory drug; PANO, panobinostat; PBO, placebo; PFS, progression-free survival.

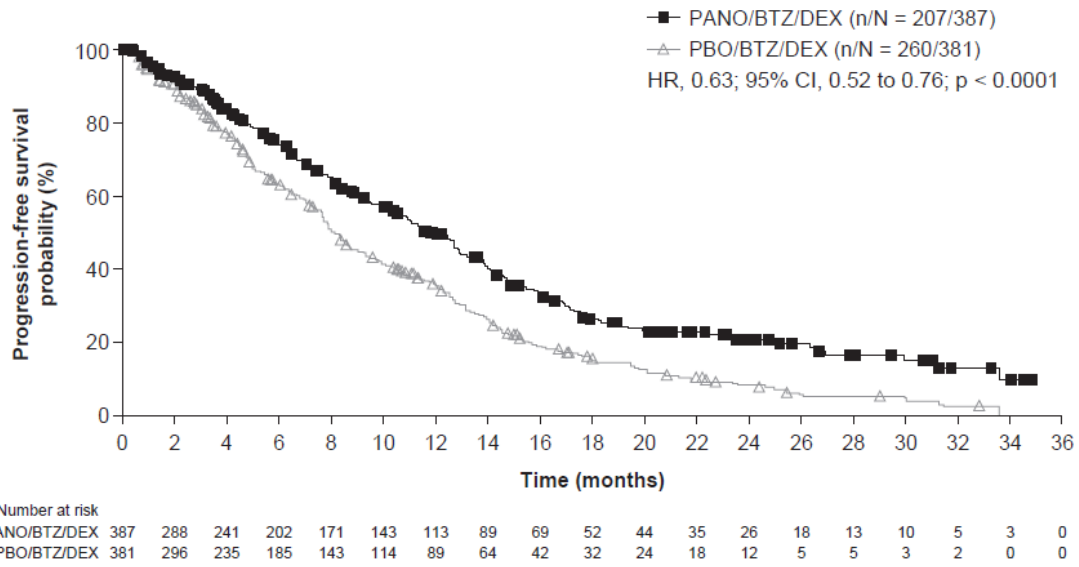
FDA 2014[30] San-Miguel et al.,2014[31]

[30] Food & Drug Administration. FDA Briefing Document Oncologic Drugs Advisory Committee Meeting, 6 November 2014.NDA 205353 panobinostat (Farydak) Novartis. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM421623.pdf. (Accessed 30 January 2015).

Source: Submission Table 13

Kaplan-Meier (KM) curves for PFS are presented in the submission for the full analysis set each trial at the data cut-off of 10 September 2013 (Figure 6 below).

Figure 6: Progression-free survival in the PANORAMA-1 study (Kaplan–Meier analysis, full analysis set, data cut-off September 2013)



BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; PANO, panobinostat; PBO, placebo

San-Miguel et al.,2014[32]

Source: Submission Figure 11

The company also present additional results of HR for PFS according to the number of prior lines of therapy. One prior line: HR, 0.69; 95% CI, 0.53 to 0.89; two prior lines: HR, 0.71; 95% CI, 0.51 to1.01, three prior lines of therapy HR, 0.46, 95% CI, 0.29, 0.72. However p values were not presented for these results.

[31] San-Miguel JF, Hungria VT, Yoon SS et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15:1195–206.

[32] San-Miguel JF, Hungria VT, Yoon SS et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15:1195–206.

They claim that other sensitivity analyses were performed and present some results in Table 14 of the submission. However they give no details on what consist the changes made within these sensitivity analysis.

Table 12: Additional sensitivity analysis for progression-free survival in the PANORAMA-1 study

	Median PFS, months		*Hazard ratio (95% CI)*
	PANO/BTZ/DEX (n = 381)	***PBO/BTZ/DEX (n = 377)***	
Per protocol investigator assessment	*12.71 (11.04 to 14.06)*	*8.08 (7.13 to 9.69)*	*0.60 (0.49 to 0.75)*
Per protocol independent review assessment	*12.71*	*7.85*	*0.59 (0.48 to 0.74)*
Patients without M-protein assessment	*12.68*	*8.08*	*0.63 (0.51 to 0.78)*

All analyses include a requirement for PD confirmation per mEBMT criteria

$p < 0$ .0001 for all sensitivity analyses

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; mEBMT, modified European Group for Blood and Bone Marrow Transplant; PANO, panobinostat; PBO, placebo; PD, progressive disease; PFS, progression-free survival.

San Miguel et al. 2014;[33]

Source: Submission Table 14

Novartis also present subgroup analysis of PFS according to prior treatment history. No p values were provided contrary to what the header of the table says.

Table 13: Subgroup analysis for progression-free survival in the PANORAMA -1 study according to randomisation strata (full analysis set)

Subgroup	*Event, %*	*Median PFS (95% CI), months*	*Cox model HR (95% CI), Log-rank p value*
All patients			
PANO/BTZ/DEX	*53.5*	*11.99 (10.32 to 12.94)*	*0.63 (0.52 to 0.76)*
PBO/BTZ/DEX	*68.2*	*8.08 (7.56 to 9.23)*	
One prior line of therapy			
PANO/BTZ/DEX	*54.5*	*12.25 (9.46 to 14.62)*	*0.66 (0.50 to 0.86)*
PBO/BTZ/DEX	*70.7*	*8.54 (7.72 to 10.41)*	
Two or three prior lines of therapy			
PANO/BTZ/DEX	*52.6*	*11.99 (9.46 to 13.70)*	*0.64 (0.50 to 0.83)*

[33] San-Miguel JF, Hungria VT, Yoon SS et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15:1195–206.

Subgroup	Event, %	Median PFS (95% CI), months	Cox model HR (95% CI), Log-rank p value
PBO/BTZ/DEX	66.2	7.62 (6.01 to 8.67)	
Prior BTZ use			
PANO/BTZ/DEX	58.0	11.04 (8.34 to 13.70)	0.58 (0.44 to 0.77)
PBO/BTZ/DEX	68.9	7.56 (5.88 to 7.89)	
No prior BTZ use			
PANO/BTZ/DEX	50.0	12.48 (10.18 to 14.16)	0.68 (0.53 to 0.87)
PBO/BTZ/DEX	67.8	8.64 (7.98 to 10.84)	

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; PANO, panobinostat; PBO, placebo; PFS, progression-free survival.

Source: Submission Table 15

Additionally an analysis of PFS results according to baseline characteristics. In most pre-specified subgroups considered PFS results favoured for the PANO group versus (vs.) the control group. It should be noted that the CI of the HR are crossing 1 for the subgroups: other ethnic origin, no previous use of IMiD drugs, Americas as geographical regions, pooled regions, normal risk of cytogenetic. However, none of the p values of the pre-specified subgroups considered are statically significant.

4.2.2. Response

The overall response rate is relatively similar for patients treated with PANO/BTZ/DEX vs. placebo/BTZ/DEX: 60.7% and 54.6%; p = 0.09. However, the proportion of patients achieving a CR or nCR was approximately two-fold higher in the PANO/BTZ/DEX group than in the placebo/BTZ/DEX group: 27.6% vs. 15.7%; p = 0.00006. Once again, the ERG is not clear why the results for PFS are only reported for 381 patients instead of 387 for the treatment arm and 377 patients instead of 381 for the control arm.

Results from a landmark analysis of data from PANORAMA-1 showed that patients achieving CR/nCR had a longer median PFS compared to patients achieving PR in both treatment groups for each time point evaluated.

Table 14: Landmark analysis for PFS response according to response status in the PANORAMA-1

Landmark time and treatment group	Number of patients		Median PFS after landmark time, months		HR (95% CI)
	with CR/nCR	with PR	Patients with CR/nCR	Patients with PR	
6 weeks					
PANO/BTZ/DEX	12	57	NE	12.55	0.33 (0.12 to 0.89)
PBO/BTZ/DEX	3	57	15.80	10.18	0.85 (0.19 to 3.90)
12 weeks					
PANO/BTZ/DEX	49	107	16.49	10.32	0.40 (0.25 to 0.65)
PBO/BTZ/DEX	23	122	14.13	9.69	0.62 (0.36 to 1.07)
18 weeks					
PANO/BTZ/DEX	76	104	16.49	10.94	0.43 (0.29 to 0.65)

Landmark time and treatment group	Number of patients		Median PFS after landmark time, months		HR (95% CI)
PBO/BTZ/DEX	*41*	*126*	*14.55*	*10.41*	*0.54 (0.35 to 0.82)*
24 weeks					
PANO/BTZ/DEX	*84*	*96*	*18.96*	*11.99*	*0.40 (0.27 to 0.59)*
PBO/BTZ/DEX	*46*	*112*	*14.88*	*11.76*	*0.57 (0.38 to 0.87)*

Analysis performed for the full analysis set and response determined according to EBMT criteria. Stratified Cox model used to obtain HR and 95% CI

BTZ, bortezomib; CI, confidence interval; CR, complete response; DEX, dexamethasone; EBMT, European Group for Blood and Bone Marrow Transplant; HR, hazard ratio; nCR, near-complete response; PANO, panobinostat; PBO, placebo; PFS, progression-free survival; PR, partial response.

Source: Submission Table 16

Novartis present various results of time to response and duration of response according to the type of response achieved by patients. The ERG asked for clarification regarding the figures in the table. The company clarified that "*the time to CR/nCR was presented incorrectly in Table 17. The median time to CR/nCR in the PAN/BTZ/DEX arm (n=107) was 2.83 months (95% CI: 2.33 months, 3.19 months), and in the BTZ/DEX arm (n=60) was 3.09 months (95% CI: 2.33 months, 3.65 months).* And that they were *seeking advice from their statisticians on the time to PR data".*

It is not clear to the ERG if the other figures presented for "*Patients achieving ≥ PR and patients achieving PR"* are correct as they remarkably differ from the corrected figures presented by Novartis in their clarification. Additionally, the number of patients is not right in Table 15 as they mentioned the full safety data set i.e. n = 381 for PANO/BTZ/DEX and n = 381 for PANO/BTZ/DEX.

Additionally the company wrote "*that the median DoR data presented in Table 17 for pts with nCR/CR, ≥ PR, and PR was correct and since has been published in EHA-3302 by P. Moreau, 2015*."[34] However the paper present the results of the landmark study presented above and in Table 14.

Table 15: Time to response and duration of response in patients achieving a PR or CR/nCR in the PANORAMA-1 study

	Time to response (95% CI), months		Duration of response (95% CI), months	
	PANO/BTZ/DEX (n = 381)	***PBO/BTZ/DEX (n = 377)***	***PANO/BTZ/DEX (n = 381)***	***PBO/BTZ/DEX (n = 377)***
Patients achieving ≥ PR according to investigator assessment	*1.51 (1.41 to 1.64)*	*2.00 (1.61 to 2.79)*	*13.14 (11.76 to 14.92)*	*10.87 (9.23 to 11.76)*

[34] European Haematology Association. Available from: http://learningcenter.ehaweb.org/eha/2015/20th/100518/philippe.moreau.analysis.of.outcomes.by.response.for.patients.with.relapsed.or.html?f=l5550p16m3

	Time to response (95% CI), months		*Duration of response (95% CI), months*	
	PANO/BTZ/DEX (n = 381)	***PBO/BTZ/DEX (n = 377)***	***PANO/BTZ/DEX (n = 381)***	***PBO/BTZ/DEX (n = 377)***
Patients achieving CR/nCR according to investigator assessment	*0.76 (0.76 to 0.95)*	*0.76 (0.72 to 0.82)*	*18.43 (15.18 to 25.56)*	*14.52 (13.40 to 18.04)*
Patients achieving PR according to investigator assessment	*1.41 (0.95 to 1.45)*	*1.41 (1.41 to 1.51)*	*9.00 (7.62 to 11.20)*	*8.77 (6.97 to 10.61)*

Analysis performed for the full analysis set and response determined according to EBMT criteria

BTZ, bortezomib; CI, confidence interval; CR, complete response; DEX, dexamethasone; EBMT, European Group for Blood and Bone Marrow Transplant; nCR, near-complete response; PANO, panobinostat; PBO, placebo; PR, partial response.

San Miguel 2014;[35]

Source: Submission Table 17

4.2.3. Treatment- free interval

In their submission, Novartis report patient median duration of treatment from the PANORAMA-1 trial. 5·0 months vs. 6·1 months for PANO/BTZ/DEX and placebo/BTZ/DEX respectively. They also report the mean duration of treatment, which were similar for both treatment groups: 6.63 months vs. 6.46 months for PANO/BTZ/DEX and placebo/BTZ/DEX respectively.

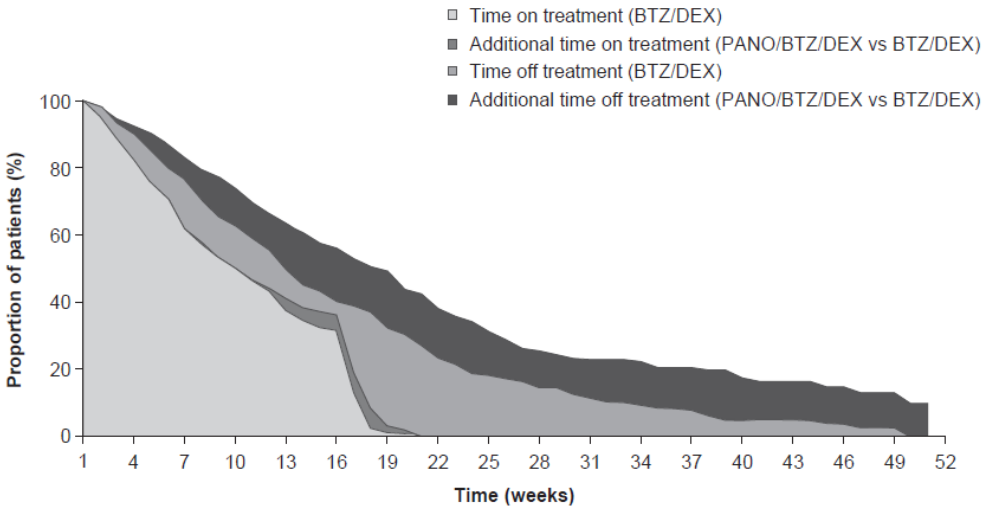
The mean time a patient remained treatment-free up to progression was longer in the PANO/BTZ/DEX group, 7.49 months (95% CI:6.05 to 8.55) compared with only 3.86 months (95% CI: 3.09 to 4.65) in the control group for the full analysis set.

For patients who achieved a CR/nCR TFI was 8.39 months for patients randomised to placebo/BTZ/DEX compared with 12.92 months for the PANO group, which represents an extension of 4.53 months.

Curves depicting time on treatment and TFI for the overall population and for patients achieving a CR/nCR in the PANORAMA-1 study are reproduced in figures below.

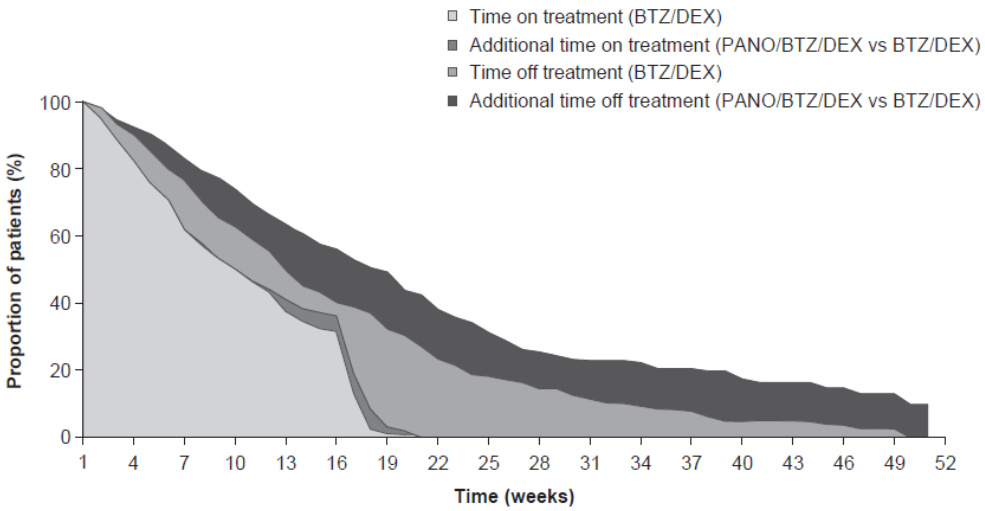
[35] San-Miguel JF, Hungria VT, Yoon SS et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15:1195–206.

Figure 7: Time on treatment and treatment-free interval for overall population in the PANORAMA-1 study



Source: Submission Figure 15

Figure 8: Time on treatment and treatment-free interval for patients achieving a CR/nCR in the PANORAMA-1 study



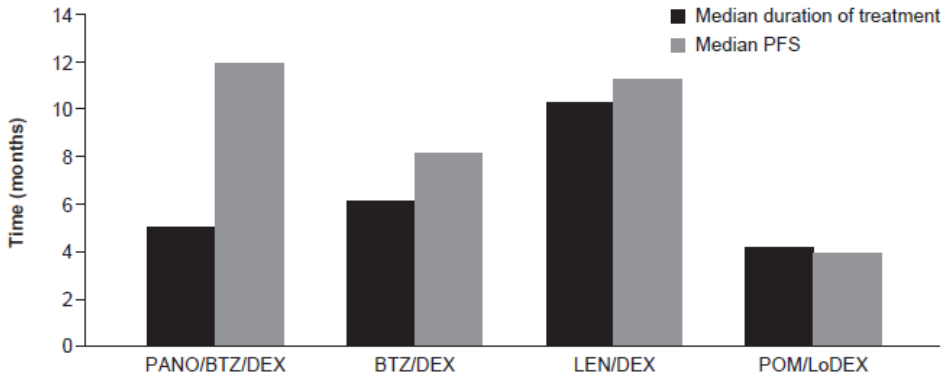
BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

Source: Submission Figure 16

Novartis compare results of the duration of exposure and TTP/PFS reported from various trials with different agents, however the ERG would like to insist that there might be many confounding factors

between the populations considered within these different trials therefore a direct comparison is not appropriate.

Figure 9: Duration of exposure and TTP/PFS reported in various trials with current standard of care novel agents



BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; LoDEX, low dose dexamethasone; PANO, panobinostat; PFS, progression-free survival; POM, pomalidomide; TTP, time to progression.

San Miguel 2014;[36] Dimopolous et al. 2007;[37] Celgene 2014;[38] San Miguel et al 2013;[39] Siegel et al 2013[40]

Source: Submission Figure 18

4.2.4. HRQL

Novartis provide HRQL scores assessed using the FACT/GOG-Ntx neurotoxicity subscale, the EORTC QLQ-MY20 and the EORTC QLQ-C30 GHS. The data is reproduced in the Figure 10 below.

[36] San-Miguel JF, Hungria VT, Yoon SS et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15:1195–206.

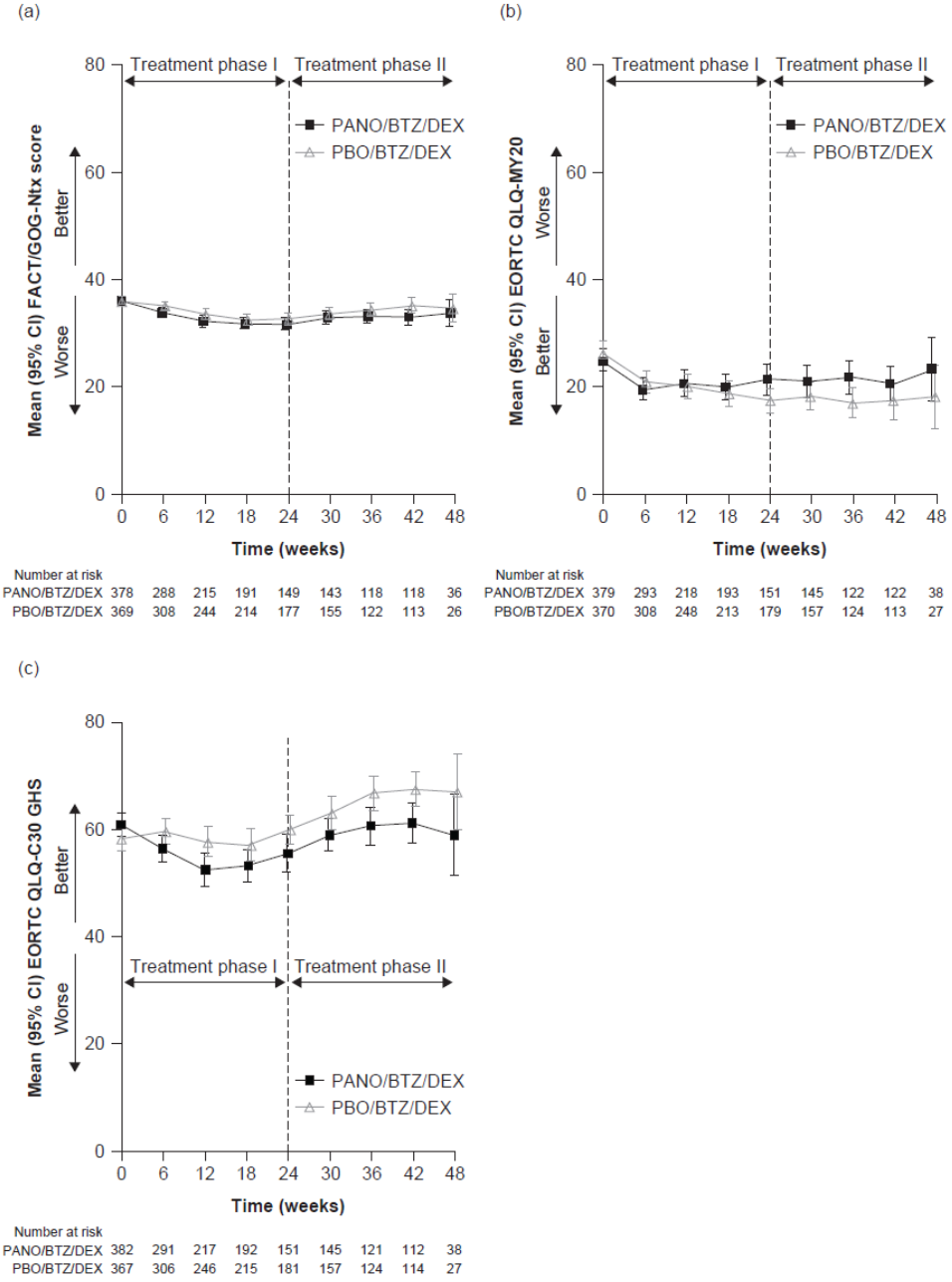
[37] Dimopoulos M, Spencer A, Attal M et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007;357 2123–32.

[38] Celgene. RevlIMiD (lenalidomide) Summary of product characteristics. Available from: https://www.medicines.org.uk/emc/medicine/19841; (Accessed 8 May 2015).

[39] San Miguel J, Weisel K, Moreau P et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. The lancet oncology 2013;14:1055–66.

[40] Siegel D, Richardson D, Dimopoulos K, al e. Efficacy and safety of pomalidomide plus low-dose dexamethasone in advanced multiple myeloma: results of randomized phase 2 and 3 trials (MM-002/MM-003) Abstract presented at American Society of Hematology annual meeting, New Orleans, LA , USA, 7-10 December 2013; Abstract 3185. Available from: http://www.bloodjournal.org/content/122/21/3185?sso-checked=true.

Figure 10: Scores for a) neurotoxitiy and b) disease-related symptoms during treatment and c) HRQL (Global Health Status) with PANO triplet therapy vs. control in the PANORAMA-1 study



BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – C30; EORTC QLQ-MY20, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma Module; FACT/GOG-Ntx, Functional Assessment of Cancer Therapy Gynecologic Oncology Group – neurotoxicity; GHS, Global Health Status; HRQL, health-related quality of life; PANO, panobinostat; PBO, placebo.

FDA 2014;[41]
Source: Submission Figure 19

The HRQL was not recorded during the TFI in PANORAMA-1. The ERG is not clear on why this is the case. The assumption made to estimate the utility value used for TFI in the cost-effectiveness analysis is explored in Section 5.2.3.4 of this report.

There is some confusion on the value cited in Section 4.7.5 of the submission which states that "*patients receiving panobinostat triplet therapy gain 0.53 quality-adjusted life year (QALY) over patients receiving BTZ/DEX*." This does not reflect "*the improved HRQL experienced during the TFI, estimated to be 0.51 (panobinostat triplet therapy) versus 0.21 (BTZ/DEX) QALY."*

4.2.5. Overall survival

OS data were provided for the two data cut-off of 10 September 2013 (first pre-planned interim analysis; corresponding to the final analysis for PFS) and 18 August 2014 (second interim analysis). It should be noted that no OS mature data have been presented in the company submission. As mentioned in Section 4.1.5 and 4.1.7 Novartis mentioned that the final analysis will be done after 415 deaths have been recorded.

Table 16: Analysis of overall survival for first and second interim analyses

	PANO/BTZ/DEX (n = 387)	*PBO/BTZ/DEX (n = 381)*	*HR (95% CI)[a] p value[b]*
First pre-planned interim analysis, 10 September 2013 data cut-off			
OS events, n (%)	*134 (34.6)*	*152 (39.9)*	*0.87 (0.69 to 1.10), p = 0.2586*
Censored, n (%)	*253 (65.4)*	*229 (60.1)*	
Kaplan–Meier estimates (95% CI), months at: *25th percentile probability* *75th percentile probability*	 *16.49 (13.63 to 20.47)* *NE*	 *15.21 (13.08 to 17.91)* *NE*	
Median OS, (95% CI), months	*33.64 (31.34 to NE)*	*30.39 (26.87 to NE)*	
Second interim analysis, 18 August 2014 data cut-off			
OS events, n (%)	*169 (43.7)*	*190 (49.9)*	*0.87 (0.70 to 1.07) p = 0.1783*
Censored, n (%)	*218 (56.3)*	*191 (50.1)*	
Kaplan–Meier estimates (95% CI), months at: *25th percentile probability* *75th percentile probability*	 *16.49 (14.55 to 21.26)* *NE*	 *15.18 (13.08 to 17.48)* *NE*	
Median OS, (95% CI), months	*38.24 (34.63 to 45.37)*	*35.38 (29.37 to 39.92)*	

[41] Food & Drug Administration. FDA Briefing Document Oncologic Drugs Advisory Committee Meeting, 6 November 2014.NDA 205353 panobinostat (Farydak) Novartis. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM421623.pdf. (Accessed 30 January 2015).

[a]Hazard ratio (HR) is obtained from stratified Cox model.
b2-sided p value is obtained from the stratified log-rank test.

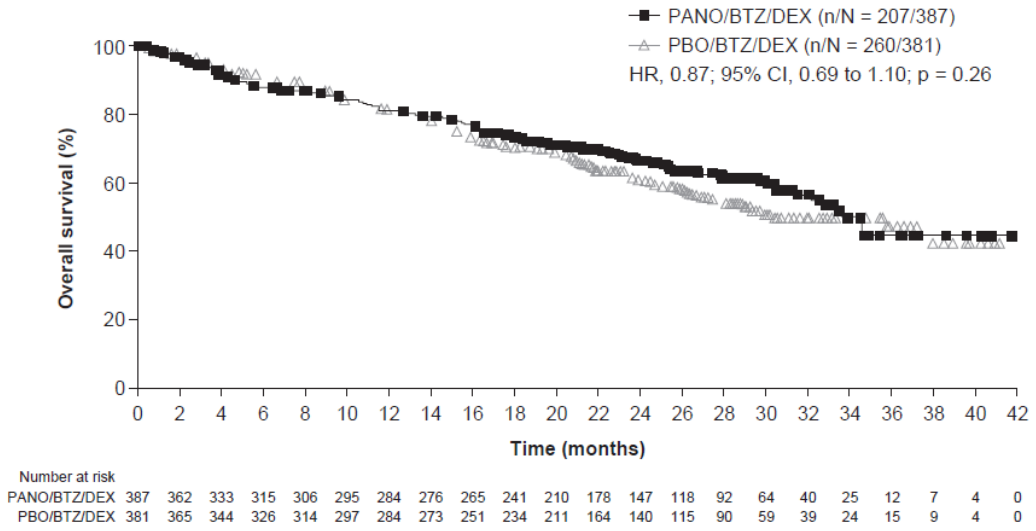
BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; NE, not estimable; OS, overall survival; PANO, anobinostat; PBO, placebo;

FDA 2014[42]

Source: Submission Table 18

Kaplan-Meier curves depicting observed OS for the full analysis set at each of the data cut-off dates are reproduced in Figure 11 and Figure 12.

Figure 11: Kaplan–Meier curve for overall survival in the PANORAMA-1 study (full analysis set, 1st interim analysis)

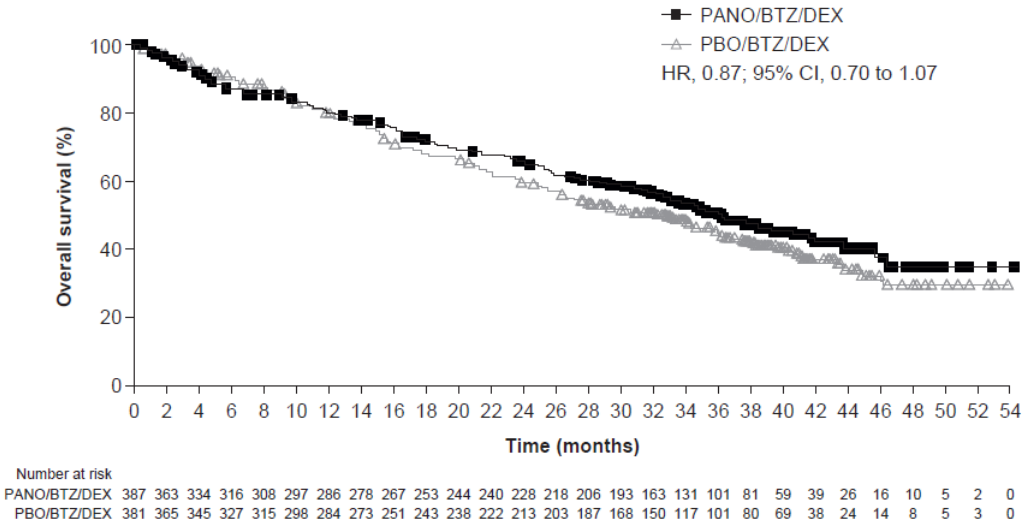


San Miguel et al. 2014; [43]

[42] Food & Drug Administration. FDA Briefing Document Oncologic Drugs Advisory Committee Meeting, 6 November 2014.NDA 205353 panobinostat (Farydak) Novartis. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM421623.pdf. (Accessed 30 January 2015).

[43] San-Miguel JF, Hungria VT, Yoon SS et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15:1195–206

Figure 12: Kaplan–Meier curve for overall survival in the PANORAMA-1 study (full analysis set, 2nd interim analysis)



BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; OS, overall survival; PANO, panobinostat; PBO, placebo.

FDA, 2014;[44]

Source: Submission Figure 21 and 22

4.2.6. AEs

In addition to the safety data reported for the phase 1b and phase 2 studies in Section 4.1.3.2, Novartis present the safety data for PANORAMA-1. Safety data have been reported for 381 patients randomised to receive PANO/BTZ/DEX and 377 patients randomised to placebo/BTZ/DEX.

Safety profile are summarised in the Table 17 below.

Table 17: AEs across randomised groups in the PANORAMA-1

Adverse event	*PANO/BTZ/DEX (n = 381)*	*PBO/BTZ/DEX (n = 377)*
Death[a] n (%)	*30 (8)*	*18 (5)*
Serious adverse events (SAEs), n (%)	*228 (60)*	*157 (42)*
Grade 3 or 4 adverse events, n (%)	*364 (96)*	*310 (82)*
Withdrawal due to adverse	*138 (36)*	*77 (20)*

[44] Food & Drug Administration. FDA Briefing Document Oncologic Drugs Advisory Committee Meeting, 6 November 2014.NDA 205353 panobinostat (Farydak) Novartis. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM421623.pdf. (Accessed 30 January 2015).

Adverse event	*PANO/BTZ/DEX (n = 381)*	*PBO/BTZ/DEX (n = 377)*
events, n (%)		
Non-haematological adverse events reported in > 10% of patients in either treatment group: any grade/grade 3 or 4, (% of patients).		
Diarrhoea	*68/25*	*42/8*
Peripheral neuropathy	*61/18*	*67/15*
Asthenia or fatigue	*57/24*	*41/12*
Nausea	*36/6*	*21/1*
Peripheral oedema	*29/2*	*19/1*
Decreased appetite	*28/3*	*12/1*
Constipation	*27/1*	*33/2*
Pyrexia	*26/1*	*15/2*
Vomiting	*26/7*	*13/1*
Cough	*21/1*	*19/0*
Insomnia	*19/0*	*16/1*
Dizziness	*19/3*	*16/2*
Upper respiratory tract infection	*18/2*	*15/2*
Pneumonia	*17/13*	*13/10*
Dyspnoea	*15/2*	*12/2*
Hypotension	*14/3*	*9/2*
Headache	*14/1*	*11/1*
Abdominal pain	*13/2*	*11/1*
Nasopharyngitis	*13/0*	*12/1*
Back pain	*13/1*	*12/1*
Dyspepsia	*12/1*	*11/0*
Upper abdominal pain	*12/1*	*10/1*
Weight decreased	*12/2*	*5/0*
Pain in extremity	*10/1*	*14/1*
Herpes zoster	*5/1*	*11/2*
Haematological adverse events reported in > 10% of patients in either treatment group: any grade/grade 3 or 4, (% of patients)		
Thrombocytopenia	*98/67*	*84/31*
Neutropenia	*75/34*	*36/11*
Anaemia	*62/18*	*52/19*
Adverse events leading to discontinuation in ≥1% of patients in either treatment group (% of patients)		
Fatigue	*2.9*	*2.9*
Diarrhoea	*4.5*	*1.6*
Asthenia	*2.9*	*0*
Pneumonia	*1.3*	*2.1*
Peripheral neuropathy	*3.7*	*1.9*
Thrombocytopenia	*1.6*	*0.5*
Infection	*5.0*	*3.7*

[a] Deaths occurring more than 28 days after the discontinuation of study treatment are not summarised

San-Miguel et al.,2014;[45] FDA 2014[46]

Source: Submission Table 34

The company present an analysis of the incidence of AEs in patients who completed cycles 9 to 12 of the study by comparing the incidence of newly occurring or worsening grade 3 / 4 AEs during cycles 9 to 12 compared with the first 8 cycles. The results are presented in the Table 18 below, The grade 3 / 4 AEs occurring in 5% or more of patients in the PANO/BTZ/DEX arm were diarrhoea (7.1% vs. 24.1% in phase 2 and 1 respectively) and thrombocytopenia (6% vs. 56.7% in phase 2 and 1 respectively).

Table 18: AEs occurring in >30% of patients in either treatment group according to treatment phase in the PANORAMA-1 study

	Treatment phase 1		*Treatment phase 2*	
AE any grade/grade 3 / 4, %	*PANO/BTZ/DEX (n = 381)*	*PBO/BTZ/DEX (n = 377)*	*PANO/BTZ/DEX (n = 168)[a]*	*PBO/BTZ/DEX (n = 193)[a]*
Diarrhoea	*65.9/24.1*	*38.2/8.0*	*29.8/7.1*	*20.2/0*
Thrombocytopenia	*64.3/56.7*	*40.1/24.4*	*18.5/6.0*	*5.2/1.0*
Anaemia	*39.9/15.5*	*31.8/15.1*	*13.7/3.0*	*9.3/3.6*
Fatigue	*39.6/16.3*	*28.9/8.8*	*8.9/1.8*	*4.7/0*
Nausea	*35.2/5.5*	*19.4/0.5*	*5.4/0*	*4.7/0*
Peripheral neuropathy	*29.4/6.0*	*32.9/4.8*	*6.5/3.0*	*11.9/1.6*
Constipation	*26.0/1.0*	*31.8/1.1*	*3.6/0*	*5.7/0*

[a]One patient randomly assigned to receive panobinostat was given placebo during cycles 1 and 2 because of a allocation error; the patient was subsequently given panobinostat from cycle 3 until discontinuation of treatment but was included in the placebo group for the safety analysis.

AE, adverse event; BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; PBO, placebo

San Miguel et al. 2014[47]

Source: Submission Table 35

4.2.7. Subgroup analysis

[45] San-Miguel JF, Hungria VT, Yoon SS et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15:1195–206.

[46] Food & Drug Administration. FDA Briefing Document Oncologic Drugs Advisory Committee Meeting, 6 November 2014.NDA 205353 panobinostat (Farydak) Novartis. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM421623.pdf. (Accessed 30 January 2015).

[47] San-Miguel J, Hungria VTM, Yoon S-S et al. Efficacy and safety based on duration of treatment of panobinostat plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma in the phase 3 Panorama 1 study. Blood 2014;124:4742.

Novartis state that analysis were conducted for two subgroups. However, Table 19 in Section 4.8, which is reproduced in Table 19 below, presents the efficacy and safety data for three subgroups but the analysis is only presented for two subgroups and compared with the overall study population:

- Group 1: Patients who received prior IMiD plus BTZ (25% of the trial sample). This group had more advanced disease compared to overall trial sample. This group was also heavily treated and previous stem cell transplantation rate was higher in comparison to the overall trial sample (76.1% vs. 57.2%);
- Group 2: Patients who received prior IMiD plus BTZ and ≥2 prior lines of treatment (19% of the trial sample).

The efficacy and safety data for the 3rd group is presented in Table 19 (along with the two other subgroups). The 3rd group is briefly mentioned in section for indirect and mixed comparisons, Table 25 b (discussed below):

- Group 3: Patients with 2 to 3 lines of treatment (48.3% of the study population).

Table 19: Efficacy and safety data for PANORAMA-1 according prior treatment compared with overall study population

	Overall study population		*Prior IMiD and BTZ*		*Prior IMiD plus BTZ and ≥ 2 prior lines of treatment,*		*2-3 prior lines of treatment*	
	PANO/ BTZ/DEX N = 387/381	***PBO/ BTZ/DEX N = 381/377***	***PANO/ BTZ/DEX N = 94/92***	***PBO/ BTZ/DEX N = 99/99***	***PANO/ BTZ/DEX N = 73/72***	***PBO/ BTZ/DEX N = 74/73***	***PANO/ BTZ/DEX N = 188/186***	***PBO/ BTZ/DEX N = 183/182***
Median PFS, months *HR (95% CI)*	*12.0* *0.63 (0.52 to 0.76)* *p < 0.0001*	*8.1*	*10.6* *0.52 (0.36 to 0.76)* *p = 0.0005*	*5.8*	*12.5* *0.47 (0.32 to 0.72)*	*4.7*	*11.30* *0.61 (0.46 to 0.80)*	*7.56*
Median OS, months *HR (95% CI)*	*38.2* *0.87 (0.70 to 1.07)* *p = 0.1783*	*35.4*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORR, % (95% CI)	*60.7, (55.7 to 65.6)*	*54.6, (49.4 to 59.7)*	*58.5 (47.9 to 68.6), p = 0.019*	*41.4 (31.6 to 51.8)*	*58.9 (46.8 to 70.3)*	*39.2 (28.0 to 51.2)*	*58.5 (51.1 to 65.6)*	*50.8 (43.3 to 58.3)*
CR/nCR, % (95% CI)	*27.6 (23.2 to 32.4)* *P = 0.00006*	*15.7 (12.2 to 19.8)*	*22.3 (14.4 to 32.1)*	*9.1 (4.2 to 16.6)* *P = 0.012*	*21.9 (13.1 to 33.1)*	*8.1 (3.0 to 16.8)*	*22.3 (16.6 to 29.0)*	*10.4 (6.4 to 15.7)*
Median duration of response, months	*13.14 (11.76 to 14.92)*	*10.87 (9.23 to 11.76)*	*12.0*	*8.3*	*11.99 (9.69 to 13.37)*	*6.97 (4.86 to 13.40)*	*N/A*	*N/A*
Median TTP	*12.71 (11.30 to 14.06)*	*8.54 (7.66 to 9.72)*	*12.3*	*6.1*	*12.68 (8.34 to 14.19)*	*4.99 (3.75 to 6.80)*	*N/A*	*N/A*
On-treatment deaths, %	*7.9*	*4.8*	*6.4*	*5.1*	*6.9*	*6.8*	*N/A*	*N/A*
Grade 3 / 4 AEs, %								

	Overall study population		*Prior IMiD and BTZ*		*Prior IMiD plus BTZ and ≥ 2 prior lines of treatment,*		*2-3 prior lines of treatment*	
Thrombocytopaenia	*67.4*	*31.4*	*66.3*	*46.5*	*68*	*44*	*69.4*	*35.7*
Infections (pneumonia)	*15.7*	*12.7*	*18.5*	*14.1*	*19.4*	*16.4*	*18.3*	*14.3*
Infections (sepsis)	*6.6*	*3.7*	*4.3*	*5.1*	*2.8*	*6.8*	*3.8*	*5.5*
Diarrhoea	*25.5*	*8.3*	*30.4*	*13.1*	*33.3*	*15.1*	*33.3*	*9.9*
Asthenia/Fatigue	*23.9*	*11.9*	*25.0*	*12.1*	*26.4*	*13.7*	*25.3*	*11.5*
Haemorrhage	*4.2*	*2.4*	*3.3*	*2.0*	*2.8*	*2.7*	*4.3*	*1.1*
Neutropenia	*34.5*		*27.2*	*10.1*	*31.9*	*9.6*	*n/a*	*n/a*

AE, adverse event; BTZ, bortezomib; CI, confidence interval; CR, complete response; DEX, dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; nCR, near-complete response; ORR, overall/objective response rate; OS, overall survival; PANO, panobinostat; PBO, placebo. PFS, progression-free survival; TTP, time to progression

FDA 2014[48]; San-Miguel et al., 2014[49];

Source: Submission Table 19

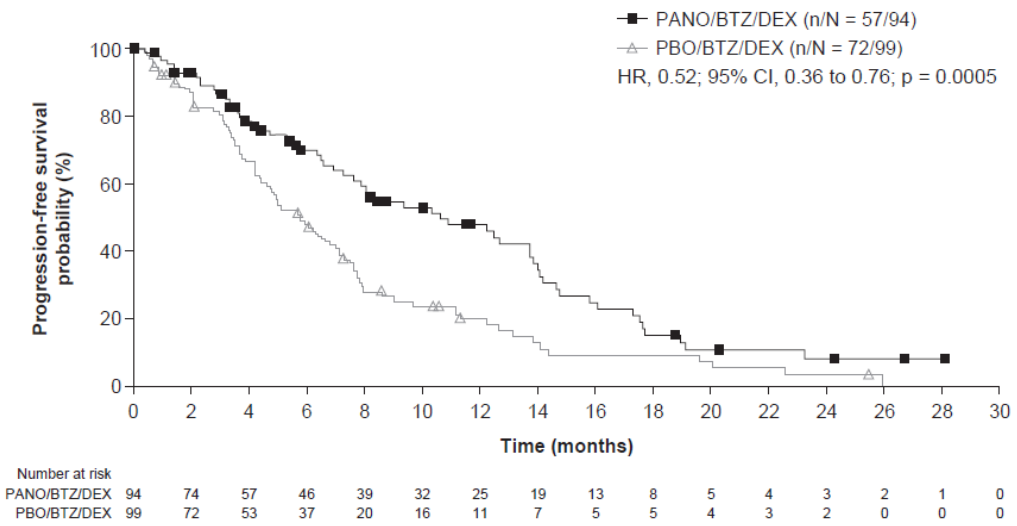
[48] Food & Drug Administration. FDA Briefing Document Oncologic Drugs Advisory Committee Meeting, 6 November 2014.NDA 205353 panobinostat (Farydak) Novartis. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM421623.pdf. (Accessed 30 January 2015).

[49] San-Miguel JF, Hungria VT, Yoon SS et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15:1195–206

Group 1

The company state that the benefit achieved with PANO/BTZ/DEX over the control arm was greater in this subgroup than in the overall population. PFS was prolonged by 4.8 months (from 5.8 months to 10.6 months). The Kaplan-Meir curves are wrongly titled and refer to subgroup analysis (Group 1) and not to full set. They are reproduced in 13 and Figure 14 below.

Figure 13: Progression-free survival in the PANORAMA-1 for patients who had received prior IMiD and BTZ therapy (Kaplan–Meier analysis, full analysis set, data cut-off September 2013)



BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; PANO, panobinostat; PBO, placebo.

Source: Submission Figure 23

Figure 14: Kaplan–Meier curve for overall survival in the PANORAMA-1 study for patients who had received prior IMiD and BTZ therapy (full analysis set, 2nd interim analysis)

[redacted]

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; PANO, panobinostat; PBO, placebo.

Source: Submission Figure 24

In terms of safety profile, the company state that it was consistent with the "*overall population or slightly more favourable"*. Novartis stated that in the control group there were a higher rate of grade 3 / 4 thrombocytopenia and grade 3 / 4 infections in patients who received prior BTZ and IMiDs compared patients who have not received prior BTZ and IMiDs. The number on- treatment deaths were comparable in two groups (PANP/BTZ/DEX vs. PBO/BTZ/DEX). Also, "a*n analysis of the relative risk of experiencing adverse events in the panobinostat group versus the control group revealed a more favourable safety profile in patients who had previously received IMiD and bortezomib compared with the total study population"*.

Group 2

It is stated that most of the patients in the UK receive IMiD and BTZ as separate lines of treatment. Most patients in England and Wales who have previously received therapy with IMiD and BTZ have received at least 2 prior lines of therapy. It is stated that median PFS was extended by 7.8 months under PANO/BTZ/DEX relative to PBO/BTZ/DEX, but the company did not present the range.

The OS was extended by [redacted] months from [redacted] months in PANO/BTZ/DEX to [redacted] months PBO/BTZ/DEX.

Novartis present the Kaplan-Meir curves of the two cut-off dates.

Figure 15: Progression-free survival in the PANORAMA-1 study for patients who had received prior IMiD and BTZ therapy and at least two lines of therapy (data cut-off September 2013)

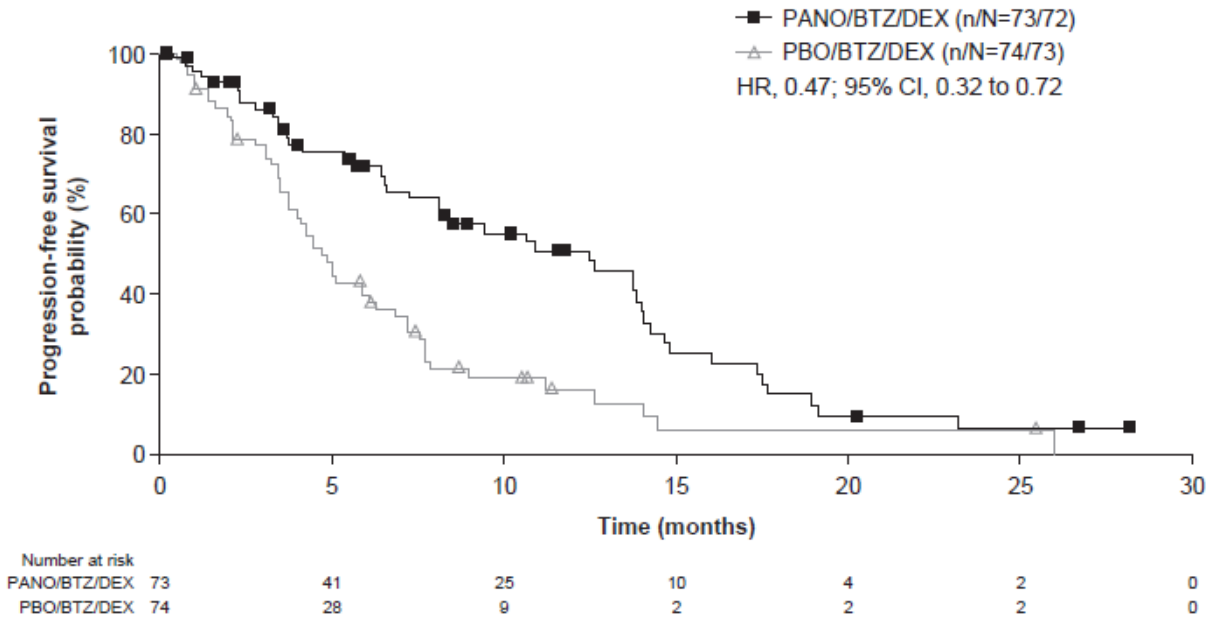


Figure 16: Kaplan–Meier curve for overall survival in the PANORAMA-1 study for patients who had received prior IMiD and BTZ therapy and at least two lines of therapy (2nd interim analysis)

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; PANO, panobinostat; PBO, placebo.

Source: Submission Figure 26 and 27

As noted above, no information is presented on Group 3.

4.3. Indirect and mixed treatment comparison

Since there was no evidence which allowed a direct comparison between PANO/BTZ/DEX and LEN/DEX, Novartis undertook an indirect treatment comparison in order to estimate the relative effectiveness between those two treatments.

4.3.1. Description of company's search strategy and comment on whether the search strategy was appropriate

In addition to the full trial sample analysis, Novartis presented a separate cost-effectiveness analysis for the PANORAMA-1 trail subpopulation, i.e. the patients who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen (see Section 6 of this report). There was no separate search strategy latter analysis; the search strategy is the same as for the direct comparison between PANO/BTZ/DEX and BTZ/DEX. The search strategy for the economic analysis will be reviewed in Section 6 in this report.

4.3.1.1. Clinical Effectiveness searches

This analysis relies on searches conducted for the full trial sample.

As noted above, separate searches for indirect and/or mixed treatment comparators were not undertaken for this submission. The ERG note however that the range of comparators used in the literature searching is broader than required in the scope.

4.3.2. Studies included and excluded

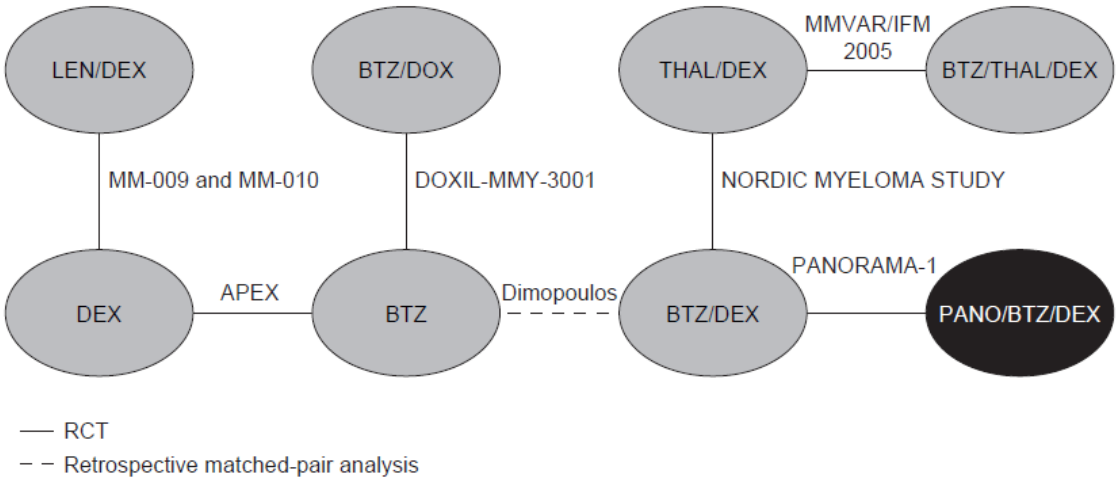
As noted in Section 4.1.2 only one RCT (PANORAMA-1 trial) was identified as direct head-to-head comparison of PANO/BTZ/DEX with other regimens.

LEN/DEX was assumed to be a relevant compactor to PANO/BTZ/DEX in the third line or later. This treatment regimen is for rrMM setting. In the economic analysis that compare PANO/BTZ/DEX to LEN/DEX efficacy, Novartis undertook the following approaches:

- Common comparators method;
- Naïve comparison;
- Unadjusted Cox regression;
- Matching adjusted indirect treatment comparison (MAIC).

Multi arm RCTs were linked via common comparators using common comparator method. The figure below presents preliminary evidence network.

Figure 17: Preliminary evidence network



Source: Submission Figure 28

The trials were assessed by the company in terms of:

- Design such as patient selection criteria;
- Patient characteristics such as age, time since diagnosis, number of prior therapies.

Using common comparators method, the company identified two trials that were both subsequently excluded: one study compared THAL/DEX to BTZ/DEX; and second study compared BTZ/THAL/DEX to THAL/DEX. The rationale for exclusion of two studies are presented in Table 20 below.

Table 20: Rationale for exclusion of two studies from the final network

Study/Reference	*Comparison*	*Rationale for exclusion*
NORDIC MYELOMA study[50]	*THAL/DEX versus BTZ/DEX*	*1) Included patients must have been refractory to melphalan* *2) THAL/DEX is not considered a valid comparator in the UK as it is not included in the draft Chemotherapy Algorithm (v.7),*[79] *or the BCSH Guidelines*[51] *3) In the HMRN audit no patients received THAL/DEX as third or fourth-line therapy.*[52]
MMVAR/IFM-2005[53]	*BTZ/THAL/DEX (ie*	*1) The trial involved patients who had progressed or relapsed after*

[50] Hjorth M, Hjertner O, Knudsen LM et al. Thalidomide and dexamethasone vs. bortezomib and dexamethasone for melphalan refractory myeloma: a randomized study. Eur J Haematol 2012;88 485–96.

[51] Bird JM, Owen RG, D'Sa S et al. Guidelines for the diagnosis and management of multiple myeloma 2014. Available from: http://www.bcshguidelines.com/documents/MYELOMA_GUIDELINE_Feb_2014_for_BCSH.pdf. (Accessed 4 June 2014).

[52] Haematological Malignancy Research Network. Clinical management and outcome of myeloma. Version 3.0.

Study/Reference	Comparison	Rationale for exclusion
	VTD) versus THAL/DEX	one ASCT and it must have been their first relapse 2) The draft (v.7) Chemotherapy Algorithm[54] recommends use of VTD as an induction treatment prior to SCT in line with NICE TA331.[55] 3) NICE Guidelines (TA129, TA228)[5657] exclude the use of THAL/BTZ 4) THAL/DEX is not considered a valid comparator in the UK as it is not included in the draft Chemotherapy Algorithm (v.7),[58] or the BCSH Guidelines[59]

Source: Submission Table 20

Therefore Novartis included 5 studies in the analysis. However, it is not very clear to the ERG how these five studies were identified. These five studies are also presented in Section 3.7 Table 5 which makes a reference to response rates to different regimens. These 5 studies are:

- *"PANORAMA-1, the pivotal phase 3 study for panobinostat (n = 768), provides data for PANO/BTZ/DEX versus BTZ/DEX[60]";*
- *"Pooled data from the MM-009 and MM-010 trials, the two pivotal phase 3 studies for lenalidomide (n = 704) provide data for LEN/DEX versus dexamethasone[616263]";*

[53] Garderet L, Iacobelli S, Moreau P et al. Superiority of the triple combination of bortezomib-thalidomide-dexamethasone over the dual combination of thalidomide-dexamethasone in patients with multiple myeloma progressing or relapsing after autologous transplantation: the MMVAR/IFM 2005-04 Randomized Phase III Trial from the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2012;30:2475–82

[54] National Chemotherapy Algorithms. Multiple myeloma. Available from: https://www.engage.england.nhs.uk/consultation/specialised-services-consultation/user_uploads/chemothrpy-algrthms-mltpl-myeloma.pdf ; (Accessed 8 May 2015).

[55] National Institute for Health and Care Excellence. Technology Appraisal 311: Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation. April 2014. Available from: https://www.nice.org.uk/guidance/ta311. (Accessed 5 June 2014).

[56] National Institute for Health and Care Excellence. Technology Appraisal 228: Bortezomib and thalidomide for the first-line treatment of multiple myeloma. July 2011. Available from: https://www.nice.org.uk/guidance/ta228. (Accessed 5 June 2014).

[57] National Institute for Health and Care Excellence. Technology Appraisal 129: Bortezomib monotherapy for relapsed multiple myeloma. October 2007. Available from: www.nice.org.uk/TA129. (Accessed 4 October 2013).

[58] National Chemotherapy Algorithms. Multiple myeloma. Available from: https://www.engage.england.nhs.uk/consultation/specialised-services-consultation/user_uploads/chemothrpy-algrthms-mltpl-myeloma.pdf; (Accessed 8 May 2015).

[59] Bird JM, Owen RG, D'Sa S et al. Guidelines for the diagnosis and management of multiple myeloma 2014. Available from: http://www.bcshguidelines.com/documents/MYELOMA_GUIDELINE_Feb_2014_for_BCSH.pdf. (Accessed 4 June 2014).

[60] San-Miguel JF, Hungria VT, Yoon SS et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15:1195–206.

- *"DOXIL-MMY-3001, a phase 3 study assessing the benefit of the addition of doxorubicin (n = 646), provides data for BTZ/DOX versus bortezomib[64]";*
- *"APEX, the pivotal phase 3 trial for bortezomib (n = 669), provides data for bortezomib versus high-dose dexamethasone[65]";*
- *"A retrospective matched-pair analysis of data for 218 patients provides data for BTZ/DEX versus bortezomib[66]";*

These studies were said to be similar in design such as patient selection criteria. The patient characteristics were similar in terms of median age, disease duration, proportion of patients with 1 prior line of therapy, "*except for the matched pairs analysis, where only patients with one prior line of therapy were considered"*. In total 3005 patients were included in the studies. The evidence network for the common comparator method is presented below.

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[61] Dimopoulos M, Spencer A, Attal M et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007;357 2123–32.

[62] Dimopoulos MA, Chen C, Spencer A et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia 2009;23:2147–52.

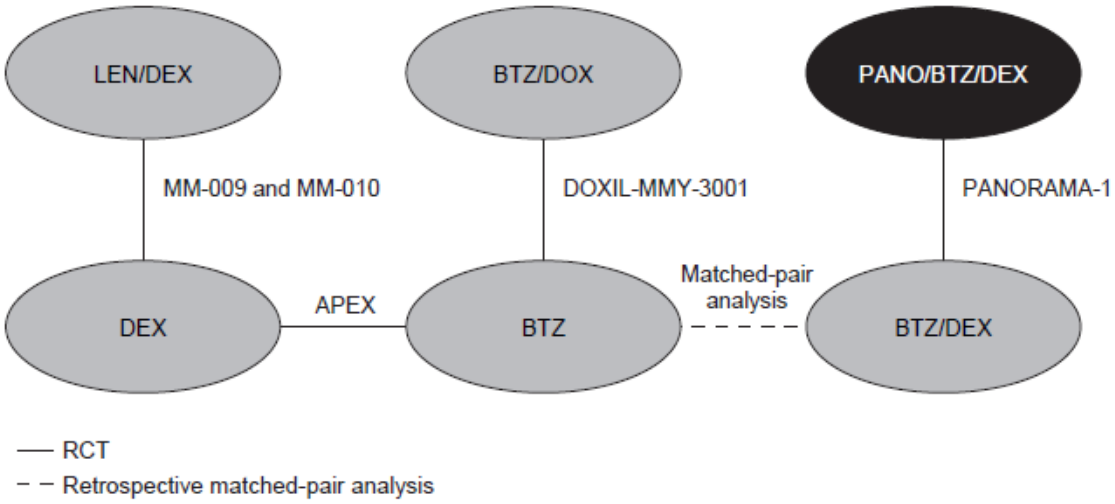
[63] Weber DM, Chen C, Niesvizky R et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357 2133–42.

[64] Orlowski RZ, Nagler A, Sonneveld P et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. J Clin Oncol 2007;25:3892–901.

[65] Richardson PG, Sonneveld P, Schuster MW et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005;352:2487–98.

[66] Dimopoulos MA, Orlowski RZ, Facon T et al. Retrospective matched-pair analysis of the efficacy and safety Of bortezomib plus dexamethasone versus bortezomib monotherapy in patients (Pts) with relapsed multiple myeloma (MM). Poster presented at the 55th ASH Annual Meeting and Exposition, 7–10 December 2013, New Orleans, Louisiana, USA.

Figure 18: Evidence network for the common comparator method



Source: Submission Figure 29

Statistical assessment of heterogeneity was not conducted as there was only one trial per treatment except for LEN/DEX who had two different trials MM-009 and MM-010. An assessment of heterogeneity could have been conducted. The ERG note that both trials were used as pooled data to provide data for LEN/DEX vs. DEX. However, it should be noted that the MM-009 population was mainly enrolled from sites in the USA and Canada. Therefore some population characteristics (like ethnicity) are potentially different from the average UK population. MM-010 enrolled patients mainly from Europe hence this typically reflects the UK population in a better fashion.

The company also stated that cyclophosphamide/THAL/DEX (CTD) is another possible comparator in the 3rd line or later (*according to the NICE scope*). It is not clear to which scope the company refer to. In addition, Novartis stated that CTD is used in 10% of patients in the 3rd line or 4th line[67]. The company stated that they sought research relevant clinical effectiveness on CTD and mentioned their search strategy which is discussed in Section 4.1.1 of this report. However, the ERG noticed that the strategy does not include terms for cyclophosphamide.

Novartis then mentioned that *"no RCTs investigating CTD in relevant patients populations were identified, single-arm studies were also considered".* The company identified *one* single-arm study investigating CTD however, *"given the small patient population (n = 53) and the significant differences in*

[67] Haematological Malignancy Research Network. Clinical management and outcome of myeloma. Version 3.0.

baseline characteristics compared with PANORAMA-1", it was decided not to include CTD as a comparator in the economic assessment.

4.3.3. Description and critique of the methods and outcomes of included studies

As stated above, four different methodologies were used for indirect treatment comparisons although Novartis state on page 98 that three methods were used. The summary of the used methods is presented in the table below.

Table 21 Summary of the methods used for indirect treatment comparison and the advantage and disadvantages of the methodologies as used in this analysis

	Common comparators method	*Naive comparison*	*Unadjusted Cox regression*	*Matching adjusted indirect treatment comparison (Cox regression)*
Comparators considered	*BTZ/DEX, BTZ, DEX, LEN/DEX, BTZ/DOX*	*LEN/DEX*	*LEN/DEX*	*LEN/DEX*
Study population employed in the comparison	*ITT population*	*ITT population; 2 to 3 prior lines of treatment*	*ITT population; 2 to 3 prior lines of treatment*	*ITT population; 2 to 3 prior lines of treatment*
Adjustment to patient population differences	*Implicitly assumes that relative efficacy measures are comparable*	*No adjustment for patient characteristics*	*No adjustment for patient characteristics*	*PANORAMA-1 population was adjusted to the MM-009/010 populations in terms of patient selection and baseline patient/ disease characteristics*
Data type used	Aggregate data	Aggregate data	• *Patient level data (PANO/BTZ/DEX)* • *Simulated patient level data for OS and PFS (LEN/DEX)*	• *Patient-level data (PANO/BTZ/DEX)* • *Simulated patient level data for OS and PFS (LEN/DEX)* • *Aggregate data for baseline characteristics (LEN/DEX)*
Advantages of the methodology	Established methodology	Simple and transparent	• *Use of patient level data* • *Patient numbers are not affected by matching*	• *Can adjust for baseline characteristics including relative treatment effect modifiers* • *By matching patient populations this approach mimics randomisation*
Disadvantage	• *Assumes factors that may influence*	• *No randomisation*	• *Assumes proportional*	• *Does not adjust for unobserved*

	Common comparators method	Naive comparison	Unadjusted Cox regression	Matching adjusted indirect treatment comparison (Cox regression)
	the relative treatment effect (eg, HR) are balanced across the trials in the evidence network • *May be large uncertainty around the outcomes as observed in this case for LEN/DEX versus PANO/BTZ/DEX)*	• *No adjustment to differences in patients or in trial design between studies*	*hazard assumption which may not be true*	*differences between trials* • *Matching performed only for shared variables* • *Assumes proportional hazard assumption which may not be true*
Outcomes compared (relative efficacy measure)	• *PFS (HR)* • *TTP (HR)* • *CR/nCR (OR)* • *OS (HR)*	• *PFS (HR)* • *OS (HR)*	• *PFS (HR)* • *OS (HR)*	• *PFS (HR)* • *OS (HR)*
Context applied in health economic model	• *Third line treatment*	• *Third line treatment*	• *Third line treatment*	• *Third line treatment*

Source: Submission Table 22

4.3.3.1. Common comparators method

As described in the submission, this method *relies on the randomisation within each trial that compared the treatment directly and using the relative effect measures for analysis. This method thus separates the true efficacy of a drug from possible placebo effects.*

The fixed-effects models were used to estimate HR of:

- PFS;
- TTP;
- OS.

And the odds ratios of:

- CR/nCR.

The summary of data used in common comparators method is summarised in the table below. Notably, no p value is presented for the HR of PFS of Matched-pairs analysis study. In addition, as noted by Novartis, the HR used for PFS is the same as the one used for TTP for the APEX study as no PFS were recorded.

Table 22: Summary of data used in the indirect treatment comparison

Study	Arm 1	Arm 2	No of patients (Arm1 /Arm 2)	HR of PFS	HR of TTP	No of patients with CR or nCR (Arm1 /Arm2)	HR of OS
PANORAMA-1[a]	PANO/ BTZ/DEX	BTZ/ DEX	387/381	0.630[b]	0.602[b]	107/60	0.87
Matched-pairs analysis	BTZ/DEX	BTZ	109/109	0.595	0.394[b]	11/9	0.958
APEX[a]	BTZ	DEX	315/312	0.550[b]	0.550[b,c]	41/5	0.570
MM-009[*]	DEX	LEN/ DEX	177/176	2.970[b]	2.822[b]	3/43	0.440
MM-010[*]	DEX	LEN/ DEX	176/175	2.567[b]	2.850[b]	9/43	0.660
DOXIL-MMY-3001[*,a]	BTZ	BTZ/ DOX	324/322	1.690[b]	1.820[b]	33/42	1.410

* The inverse of the hazard ratio (control arm versus experimental arm) was reported.

[a] BTZ was administered intravenously in the studies.

[b] $p < .05$.

[c] HR not reported; assumed to be the same as HR of TTP.

Source: Submission Table 23

The company state that models were conducted using Markov chain Monte Carlo simulations implemented in WinBUGS 1.4. However, Novartis failed to provide the ERG with the WinBUGS files. Therefore, the ERG is concerned with the validity of these analyses and cannot comment on their quality.

The summary of the results of common comparators method is presented in the table below.

Table 23: Summary of the results of the indirect treatment comparison (common comparators method)

	PANO/BTZ/DEX	BTZ/DEX	BTZ	DEX	LEN/DEX	BTZ/DOX
PFS HR (± CrI)[a]	1.00	1.60 (1.32 to 1.92)	2.77 (1.54 to 4.62)	5.11 (2.51 to 9.20)	1.87 (0.87 to 3.49)	1.66 (0.87 to 2.90)
TTP HR (± CrI)[b]	1.00	1.67 (1.37 to 2.01)	2.92 (1.60 to 4.95)	5.40 (2.62 to 10.00)	1.91 (0.90 to 3.60)	1.61 (0.83 to 2.85)
CR/nCR (± CrI)[c]	1.00	0.50 (0.34 to 0.69)	0.44 (0.14 to 1.04)	0.05 (0.01 to 0.15)	0.49 (0.08 to 1.63)	0.60 (0.17 to 1.51)
OS (± CrI)[d]	1.00	1.15 (0.91 to 1.45)	1.25 (0.65 to 2.19)	2.23 (1.03 to 4.16)	1.22 (0.53 to 2.39)	0.91 (0.42 to1.72)

[a] Values > 1 indicate shorter PFS than for PANO/BTZ/DEX.

[b] Values > 1 indicate shorter TTP than for PANO/BTZ/DEX.

[c] Values < 1 indicate lower rate of CR + nCR than for PANO/BTZ/DEX.

[d] Values > 1 indicate shorter OS than for PANO/BTZ/DEX.

Source: Submission Table 24

According to the common comparator method, *"PANO/BTZ/DEX triplet therapy [was] shown to be superior to all five comparator regimens for PFS, TTP and CR/nCR".* The company claim that the differences were statistically significant for all comparisons except for PANO/BTZ/DEX vs. LEN/DEX and BTZ/DOX.

Despite the fact that PANORAMA-1 OS data is not yet mature, the company state that *"the analysis indicated a more favourable OS for PANO/BTZ/DEX for all comparators except for BTZ/DOX, although differences were not statistically significant except against dexamethasone monotherapy".* Again, the ERG is unable to comment on the validity of this claim as no original WinBUGS files with which to check the statistical model specification were submitted for assessment.

Although 2 to 3 prior lines of treatment subpopulations were analysed using the three other indirect comparison methods, no results were presented for this subpopulation in the common comparisons analysis. No explanation was presented on why this is the case.

4.3.3.2. Naïve comparison

Naïve comparison was conducted to analyses only the PFS and OS outcomes by comparing MM-009/010 trials to the PANORAMA-1 arms. There is no clear explanation on why only those two studies were selected for the naïve comparison.

This method assumes exponential survival models for PFS and OS. There were no CI presented for the HRs of PFS and OS as the company state that it was not reported in MM-009 and MM-010 trials. However, this potentially could raise a concern on the statistical significance of the presented findings. The PFS and OS HRs are presented for the full data set of PANORAMA-1 and the subgroup of patients who received 2 to 3 prior lines of therapy. The latter subgroup is then analysed in the Appendix 17 of the submission. Novartis did not present any Kaplan-Meir curves for the naïve comparison.

The summary of the data used and the resulting HRs for the full data set is presented below.

Table 24: HR for full data set – Naïve comparison

	PANO/BTZ/DEX	*LEN/DEX*	*Hazard ratio (LEN/DEX versus PANO/BTZ/DEX)*
PFS, months	*12.0*	*11.1*	*1.081*
OS, months	*38.24*	*38.0*	*1.006*

Source: Submission Table 25a

The next table corresponds to the subgroup of patients who received 2 to 3 prior lines of treatment.

Table 25: HR for subgroup population – Naïve comparison

	PANO/BTZ/DEX	LEN/DEX	Hazard ratio (LEN/DEX versus PAN/BTZ/DEX)
PFS, months	*11.3*	*9.5*	*1.19*
OS, months	[redacted]	*35.8*	*0.959*

Source: Submission Table 25b

4.3.3.3. Unadjusted Cox regression

Although the company do not specify which studies are included in the indirect comparison method, the ERG assume that these are the MM-009 and MM-010 trials. This method was used to analyse only the PFS and OS outcomes by comparing LEN/DEX to PANO/BTZ/DEX for the full data set and the subpopulation who received 2 to 3 prior lines of treatment.

Patients who received prior LEN based treatment in the PANORAMA-1 trial were excluded from the analysis. Novartis do not give any explanation to why this was done. Patients who received prior LEN based treatment in the PANORAMA-1 trial were not excluded in common comparator analysis and Naïve comparison when looking at PANO/BTZ/DEX vs. LEN/DEX. Furthermore, in the MAIC analysis description, under Table 27, Novartis state: "*The MM-009/MM-010 trials excluded patients who had previously received LEN. Therefore, to match the patient selection criteria, PANO/BTZ/DEX patients who had received prior LEN/DEX were excluded from the analysis set (n = 315). A further patient was excluded due to lack of complete information on all covariates (n = 314)*". This type of exclusion was not, however, mentioned in other analyses; therefore, ERG cannot endorse the validity and generalisability of the presented efficacy results to the patient population of interest to this assessment.

The company state that individual patient level data was simulated for LEN/DEX. However, Novartis fail to give any further details on the method employed, therefore the ERG would like to raise a concern on this matter. Moreover, since no CI intervals were presented for the HR results, the estimated relative effects may be simply the result of a chance finding rather than a representation of true efficacy.

The tables below summarises the HR for the full data set and the subpopulation who received 2 to 3 prior lines of treatment.

Table 26: HR for full data set – Unadjusted Cox regression

Efficacy outcome	Hazard ratio (LEN/DEX versus PANO/BTZ/DEX)
Progression-free survival	*1.062*
Overall survival	*1.020*

Source: Submission Table 26a

Table 27: HR for subgroup population – Unadjusted Cox regression

Efficacy outcome	Hazard ratio (LEN/DEX versus PAN/BTZ/DEX)

Efficacy outcome	Hazard ratio (LEN/DEX versus PAN/BTZ/DEX)
Progression-free survival	*1.061*
Overall survival	*1.075*

Source: Submission Table 26b

The results presented for the Unadjusted Cox the full data in Table 26a are incorrect as they do not match the results presented in the Kaplan Meier curves below. Therefore the Table for the analysis of the full data set should be as below.

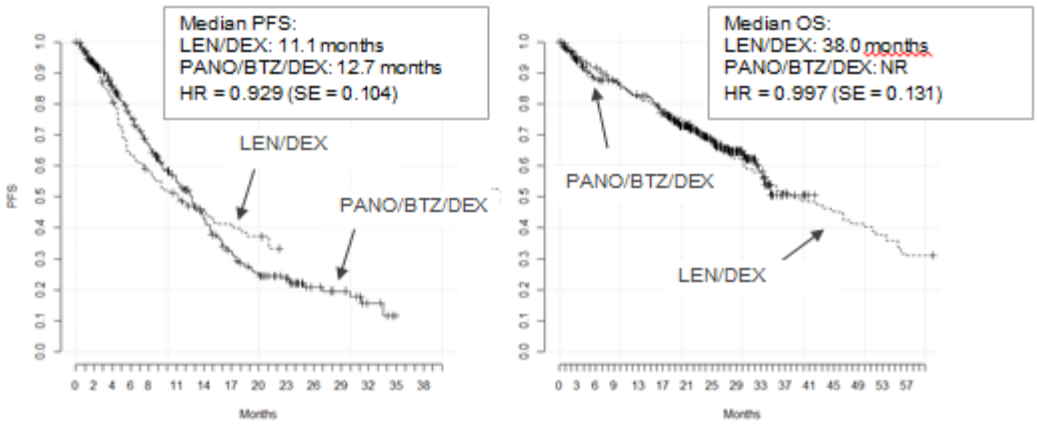
Table 28: HR for full data set – Unadjusted Cox regression

Efficacy outcome	Hazard ratio (LEN/DEX versus PANO/BTZ/DEX)
Progression-free survival	**0.929**
Overall survival	**0.997**

Sourced: Submission Table 26a corrected by the ERG

The Kaplan-Meir curves were presented in this analysis and are reported below.

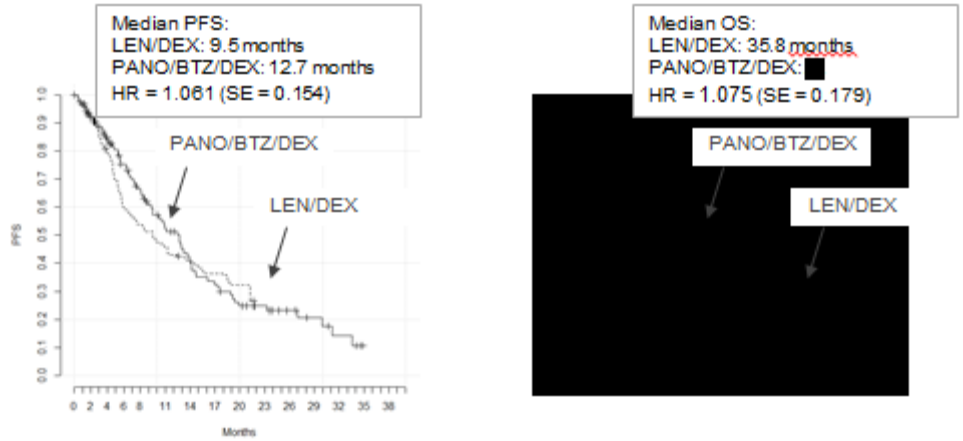
Figure 19: Kaplan–Meier curves for LEN/DEX vs. PANO/BTZ/DEX for full data set - Unadjusted Cox regression



N = 353 for LEN/DEX, N = 314 for PANO/BTZ/DEX

Source: Submission Table 26a

Figure 20: Kaplan–Meier curves for LEN/DEX vs. PANO/BTZ/DEX for the subpopulation 2 to 3 prior lines



N = 220 for LEN/DEX, N = 142 for PANO/BTZ/DEX

Source: Submission Table 26b

A simple visual inspection of any of the charts in this section shows that the shapes of the Kaplan-Meier curves for the two arms being compared do not meet the criteria to the parallel pattern implied by the proportional hazards assumption.[68] In fact the curves cross in all instances. Therefore the hazard ratio estimate is likely to be an invalid, meaningless summary measure of the relative effectiveness.

4.3.3.4. MAIC

MAIC was performed to analyse only the PFS and OS outcomes by comparing LEN/DEX to PANO/BTZ/DEX. This method is used in indirect comparisons where no common comparators can be established and/or where adjustments for observed differences in patient populations are required. It requires patient-level data for at least one trial (or trial arm) so that their mean outcomes may be weighted by the weights that match the mean baseline characteristics to the mean characteristics of the trial (arm) sample against which it is being compared. Individual patient level data was taken from PANORAMA-1 and pooled summary data were taken from MM-009 and MM-010.

The *"aggregated level data (number of patients at risk), the Kaplan–Meier curves of PFS and OS together with the baseline patient characteristics for patients receiving LEN/DEX were used"*. The XY extract graph digitizer software (not specified) was used to read the Kaplan-Meier curves for PFS and OS. The extracted data were then used to generate the individual time to event data was generated based on a peer reviewed algorithm[69].

[68] Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching. (2014)

[69] Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9.

The matching algorithm proposed by Signorovitch et al.[70] was "*used to adjust for differences between the trials in terms of patient and disease characteristics at baseline*". Novartis claim that all available variables were used in this analysis (as presented in Table 29 and Table 30).

This method allow to match patient characteristics. The results before and after the adjustment of the PANORAMA-1 trial are presented in the tables below.

Table 29: Baseline patient characteristics used in the MAIC for full data set

Baseline characteristics, proportion of patients	*LEN/DEX (n = 353)*	*PANO/BTZ/DEX Unadjusted (n = 314)[a]*	*PANO/BTZ/DEX Adjusted (n = 137)*
Patients with median age > 63 years	*50.0%*	*53.5%*	*50.0%*
Male	*59.5%*	*53.2%*	*59.5%*
Patients with median time since diagnosis > 38.4 months	*50.0%*	*52.5%*	*50.0%*
ECOG 0	*43.1%*	*42.7%*	*43.1%*
Patients receiving ≥ 2 prior therapies	*64.9%*	*48.7%*	*64.9%*
Previous THAL	*36.0%*	*55.1%*	*36.0%*
Prior BTZ	*7.6%*	*43.0%*	*7.6%*
Prior SCT	*58.4%*	*55.1%*	*58.4%*
Serum ß2-microglobulin (> 2.5 mg/L)	*70.8%*	*71.0%*	*70.8%*

[a]The MM-009/MM-010 trials excluded patients who had previously received LEN. Therefore, to match the patient selection criteria, PANO/BTZ/DEX patients who had received prior LEN/DEX were excluded from the analysis set (n = 315). A further patients was excluded due to lack of complete information on all covariates (n = 314).
BTZ, bortezomib; DEX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; LEN, lenalidomide; PANO, panobinostat; SCT, stem cell transplant; THAL, thalidomide.
Source: Submission Table 27a

Table 30: Baseline patient characteristics used in the MAIC for subpopulation 2 to 3 prior lines

Baseline characteristics, proportion of patients	*LEN/DEX (n = xxx)*	*PANO/BTZ/DEX Unadjusted[a] (n = 142)*	*PANO/BTZ/DEX Adjusted (n = 23)*

[70] Signorovitch JE, Wu EQ, Yu AP et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. Pharmacoeconomics 2010;28:935–45.

Patients with median age > 63 years	*50%*	*48.6%*	*50%*
Male	*58.2%*	*53.5%*	*58.2%*
Patients with median time since diagnosis > 49.2 months	*50%*	*47.2%*	*50%*
ECOG 0 to 1	*85.5%*	*38.0%*	*85.5%*
Previous THAL	*51.8%*	*63.4%*	*11.4%*
Prior BTZ	*11.4%*	*59.2%*	*53.2%*
Prior SCT	*53.2%*	*56.3%*	*74.5%*
Serum ß2-microglobulin (> 2.5 mg/L)	*74.5%*	*67.6%*	*50%*

[a] The MM-009/MM-010 trials excluded patients who had previously received LEN. Therefore, to match the patient selection criteria, PANO/BTZ/DEX patients who had received prior LEN/DEX were excluded from the analysis set (n = 188). For the prior 2-3 LoT analysis, all patients had complete information on the covariates.
BTZ, bortezomib; DEX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; LEN, lenalidomide; PANO, panobinostat; SCT, stem cell transplant; THAL, thalidomide.
Stadtmauer et al., 2009;[71]

Source: Submission table 27b

There are several issues with Table 30. Firstly the company omitted to indicate the number of patients for the subpopulation with 2 to 3 prior lines of treatment for the LEN/DEX data set. They then claim that the matched analyses yielded almost equality in baseline characteristics results. In fact, the adjusted results presented are identical for all baseline characteristics but Previous THAL, Prior BTZ, Prior BTZ, Serum ß2-microglobulin (> 2.5 mg/L) in the subpopulation with 2 to 3 prior lines of treatment. It seems that the results have placed in the wrong rows, but it is not clear.

The tables below summarise the HR for the full data set and the subpopulation who received 2 to 3 prior lines of treatment. Again, no CI are presented.

Table 31: HR for full data set - MAIC

Efficacy outcome	*Hazard ratio (LEN/DEX versus PANO/BTZ/DEX)*
Progression-free survival	*1.002*
Overall survival	*1.052*

Source: Submission Table 28a

[71] Stadtmauer EA, Weber DM, Niesvizky R et al. Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma. Eur J Haematol 2009;82:426–32.

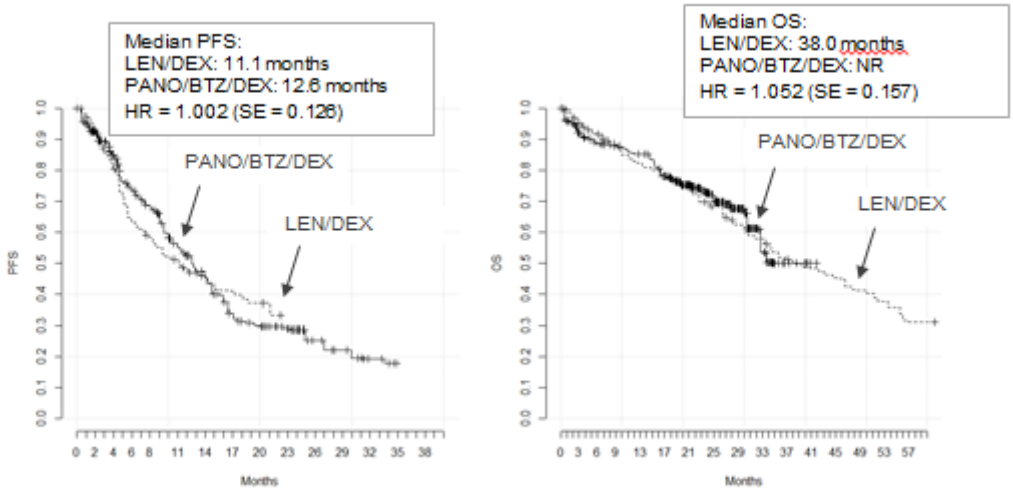
Table 32: HR for subpopulation 2 to 3 prior lines - MAIC

Efficacy outcome	*Hazard ratio (LEN/DEX versus PANO/BTZ/DEX)*
Progression-free survival	*1.108*
Overall survival	*1.413*

Source: Submission Table 28b

The Kaplan-Meir curves are presented in the submission.

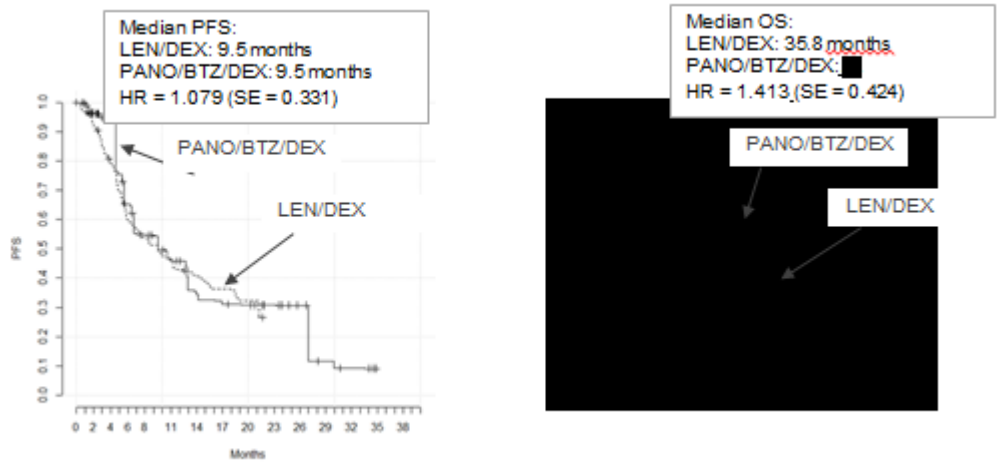
Figure 21: Kaplan-Meir curves for full data set



N = 353 for LEN/DEX, N = 137 for PANO/BTZ/DEX

Source: Submission Table 28a

Figure 22: Kaplan-Meir curves for subpopulation 2 to 3 prior lines



N = 220 for LEN/DEX, N = 22.5 for PANO/BTZ/DEX (one patient discarded after matching because of the extreme weight estimated for that patient)

Source: Submission Table 28b

Novartis present the summary of the HRs from the four analysis for the full trail population data set and the subpopulation 2 to 3 prior lines.

Table 33: Summary of four analyses – full data set

	Common comparators method	*Naive comparison*	*Unadjusted Cox*	*Matching adjusted indirect treatment comparison*
Progression-free survival	*1.870*	*1.081*	*0.929*	*1.062*
Overall survival	*1.216*	*1.006*	*0.997*	*1.020*

Source: Submission Table 29a

Table 34: Summary of four analyses – Subpopulation

	Naive comparison	*Unadjusted Cox*	*Matching adjusted indirect treatment comparison*
Progression-free survival	*1.190*	*1.061*	*1.108*
Overall survival	*0.959*	*1.075*	*1.413*

Source: Submission Table 29b

The results presented for the Unadjusted Cox and MAIC methods for the full trial population in two tables above do not match those in Table 26 and Table 31 However, when we crossed compared with the data presented in the Appendix 17 of the submission, the results appear to be wrong in Table 33 for the MAIC method. Therefore the Table should be as below.

Table 35: Summary of four analyses – full data set

	Common comparators method	*Naive comparison*	*Unadjusted Cox*	*Matching adjusted indirect treatment comparison*
Progression-free survival	*1.870*	*1.081*	*0.929*	***1.002***
Overall survival	*1.216*	*1.006*	*0.997*	***1.052***

Source: Submission Table 29a corrected by the ERG

The company state that MAIC method can only adjust for differences in baseline characteristics common to the trials. Here Novartis state that they have adjusted for several characteristics (this claim cannot be validated by the ERG as no data files were submitted for the assessment), but "*there may be some remaining differences between the patient populations that could bias the treatment comparison. In particular, the use of a different mix of subsequent antineoplastic therapies may affect the OS comparison; however this bias often applies when comparing treatments arms with a randomised controlled trial in rrMM since treatments after the randomised treatment are not specified in the study protocol*." Furthermore, the lack of patient-level data for MM009/010 trials can result in uncertainty around the findings as the simulation method used has its own procedural caveats.

Novartis suggest that the MAIC method "*provides the most appropriate approach for deriving the relative efficacies of the PANO/BTZ/DEX versus LEN/DEX for use in the economic evaluation*".

4.3.3.5. Risk of bias

In the subsequent Section 4.10.5, Novartis outline the risk of biases on these methods, but fail to present the risk of bias for the Unadjusted Cox comparison method. The company note that the results of common comparator method could be biased because the methodology used "*assumes that covariates acting as potential relative treatment-effect modifiers (eg, prior bortezomib) are balanced across trials or any heterogeneity in these risk factors does not impact the analysis results*." In addition, the estimated HR for PFS, OS and TTP assumed that the relative risk (RR) between two treatment groups remained unchanged throughout the follow-up period of the trial. Novartis, however, do not present the RR mentioned. In any case visual comparative inspection of the shape of the Kaplan-Meier survival curves for the outcomes analysed suggest that the analysis produced an invalid estimated measure of relative effectiveness.

The company also discuss the risk of bias for the naïve comparison and note that this method makes no adjustment for differences in trial design and population and assumes that these differences do not influence the HRs. It also assumes an exponential distribution for both PFS and OS which cannot be verified. As noted before, the MM-009 population was mainly enrolled from sites in the USA and Canada. Therefore some population characteristics (like ethnicity) are potentially different from the average UK population. MM-010 enrolled patients mainly from Europe hence this reflects the UK population in a better fashion.

A visual inspection of the Kaplan-Meier curves for the two arms being compared by Unadjusted Cox regression do not meet the criteria of the parallel pattern implied by the proportional hazards assumption.[72] In fact the curves cross in all instances. Therefore the hazard ratio estimate is likely to be an invalid, meaningless summary measure of the relative effectiveness.

Although the MAIC analyses may in principle provide the best source of point estimates of relative effectiveness in OS and PFS, the company do not provide estimates of sampling uncertainty (confidence intervals or p values) with which to judge whether the estimated effect may simply be due to chance as opposed to reflect a true effect. Although sampling uncertainty estimates were not reported, the company reported the effective sample size in the two MAIC analyses for the full population sample and for patients who received 2 or 3 prior lines of treatment at baseline. The original sample size in the PANO/BTZ/DEX arm (i.e. the number of observations that contributed to the analysis) used for the whole sample analysis was 314 and its effective sample was 137 (44%), whilst the original sample of patients with 2-3 prior lines of treatment was 142 and its effective sample size was 23 (16%). This indicates that some patients received extreme weights, particularly for the latter analysis.73 This indicates a low statistical power to detect significant differences. In summary, although these estimates may address some of the issues of the other methods used in the mixed and indirect comparison of PANO triplet therapy with other regimens, they are likely to be unreliable and biased by unobserved confounding.

4.3.4. Critique of the indirect comparison use in the cost-effectiveness analysis

In Section 4.10.6 Novartis state that HRs reported above (Table 34 and Table 35) are applied to two subgroups and make a reference to Section 4.8. However Section 4.8 of the submission described three groups and two of them are described in more depth: group 1 and 2. However the ERG are not clear where the HRs are applied within the cost-effectiveness analysis since no cost-effectiveness ratio is presented for the sub groups.

4.4. Critique of submitted evidence synthesis

Generally, evidence on clinical outcomes is distributed at various points throughout the document making it difficult to form a rounded picture of the effectiveness if treatment. Trial data on PFS, AEs and quality of life all appear at different places in the report.

[72] Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching (2014).

[73] Signorovitch JE, Wu EQ, Yu AP et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. Pharmacoeconomics 2010;28:935–45.

The use of the terms relapsed, and relapsed and refractory multiple myeloma create some confusion. The ERG is generally concerned with the impact that this may have when considering the evidence provided for the different PANO indications.

The ERG is also concerned with the efficacy data used for the control arm since the use of BTZ does not correspond with that recommended in NICE guidance and will impact on the clinical outcomes from the model. Firstly, there is no 4-cycle stopping rule for the BTZ/DEX arm in the PANORAMA-1 trial as per recommended in the NICE TA129 guidance. Secondly, patients continued treatment up to cycle 16 instead of cycle 8 as per BTZ label. This would have an impact on the clinical outcomes from the model.

The HRQL was not measured in PANORAMA-1 trial during TFI therefore it was necessary to assume that the HRQL in that state was equal to the last cycle of treatment.

Critique on efficacy outcomes:

- There are also a few issues with the reported PFS and OS. Different numbers were observed by investigator and independent review and Novartis do not provide an explanation to this. Additionally, the ERG is not clear why the results for PFS are only reported for 381 patients instead of 387 for the treatment arm and 377 patients instead of 381 for the control arm as they claim that final PFS was observed;
- The company also present a summary of sensitivity analysis around PFS, but no details on parameter changes were presented;
- Importantly, no mature OS data for the PANORAMA-1 trial have been reported in this submission.

Novartis present three subgroup population in the submission, but does not make a reference to the third group until the later stage where the indirect and mixed comparison methods are discussed, which serves as a basis for subgroup analysis of patients who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen.

One of the weaknesses of the clinical effectiveness evidence for the PNAO vs. LEN comparison is that there is no direct trial-based comparison between Len and the primary comparators defined in the scope, therefore the submission relies on indirect comparison.

Critique on the indirect and mixed treatment comparisons (Section 4.10):

- This section appears in the submission without any explanation of how it relates to the effectiveness and cost-effectiveness of PANO in relation to the main incremental analysis for the population of interest. It could be interpreted as indicating that BTZ/DEX is an inappropriate comparator of PANO/BTZ/DEX for some patients who have received at least one prior therapy. This warrants further discussion given that the authorised indication for PANO has yet to be determined;
- Novartis compare results of the duration of exposure and TTP/PFS reported from various trials with different comparators, however the ERG would like to insist that there might be many confounding

factors between the populations considered within these different trials therefore a direct comparison is not appropriate;

- Generally, the methods of indirect and mixed comparisons are poorly described. Novartis do not give many details on the methods used. The ERG is concerned with absence of the WinBUGS files as the company claimed that is what they have used for the common comparison method;
- A number tables in the section on indirect and mixed comparisons have errors and statistical significance is no systematically presented;
- Most importantly, all the evidence arising from these studies is likely to be affected by confounding, whether it is from observed differences across trials and trial arms in baseline characteristics, or unmeasured confounding. All unadjusted analyses for baseline differences are likely to be biased (including the analyses using individual patient data, which also invalidly assume proportional hazards) and the only adjusted analyses, those based on the MAIC method, suffer from low statistical power (as evidenced by the effective sample sizes).

5. Economic evaluation: full trial sample analysis – people who have received at least one prior therapy

This section deals with the cost-effectiveness analysis of the PANORAMA-1 trial full trial sample i.e. patients who have received at least one prior therapy, comparing PANO/BTZ/DEX with BTZ/DEX. Section 6 covers the cost-effectiveness of subgroup analysis of patients who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen, comparing PANO/BTZ/DEX vs. LEN/DEX. The CHMP adopted a positive opinion recommending the granting of a marketing authorisation for PANO in combination with BTZ and DEX for treatment of relapsed and/or refractory multiple myeloma for the latter subgroup[74].

We start with a summary of the systemic review of cost-effectiveness studies presented by Novartis and the methods used in the economic evaluation (Section 5.1). Then we present a critique of the methods they used (Section 5.2). This is followed by a description of Novartis' results (Section 5.3) and our comment on their validity (Section 5.4).

5.1. Overview of company's economic evaluation

5.1.1. Summary of Novartis' systematic review of cost-effectiveness studies

5.1.1.1. Description of company's search strategy and comment on whether the search strategy was appropriate

Novartis presented a literature search protocol to support its review of cost effectiveness. This protocol included systematic searches of key biomedical databases using a literature search strategy and hand searching of conference abstracts. The search protocol was last updated in December 2014.

Two literature searches were run using slightly different syntax structures:

Search one (2006-August 2013) took the following form:

1. (terms for myeloma) AND
2. (a study design search filter for costs or economic data)

Search two (April 2013- April 2014 and then April 2014-December 2014) took the following form:

[74] EMA. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003725/smops/Positive/human_smop_000846.jsp&mid=WC0b01ac058001d127 (Accessed 30/06/15)

1. (terms for myeloma) AND
2. (terms/a study design search filter for costs or economic data) AND
3. (terms for thalidomide or bortezomib or lenalidomide or pomalidomide or carfilzomib or ixazomib or panobinostat)

Literature searching for published studies was conducted in MEDLINE, MEDLINE in Process and EMBASE all via OVID. The following conference proceedings were searched 2011-May 2013: ASH, ASCO, EHA, ESMO, IMF, IMW, ISPOR and AMCP. ASH, ASCO, EHA, ESMO, IMF, IMW were searched again 2013 – May 2014.

A limit to studies published in the English language was applied and the searches were limited by date. A different date parameter was used on these searches (2006 – December 2014) compared with the review of clinical effectiveness (which used 2003-December 2014). The inclusion criteria used in the screening is presented in the table below.

Table 36: Eligibility criteria used in the screening

Variable	*Inclusion criteria*	*Exclusion criteria*
Populations	*Patients with rrMM, receiving treatment with an intervention of interest for CUA studies* *Patients with MM for cost analysis and resource use studies*	*CUA where rrMM-specific results cannot be clearly separated from other data*
Interventions	*Panobinostat* *Thalidomide* *Lenalidomide* *Bortezomib* *Pomalidomide* *Carfilzomib* *Ixazomib*	*Specific first-line therapies or ASCT*
Outcomes	*Study must contain at least one of the following:* *ICERs* *cost per clinical outcome* *total QALYs* *total LYGs* *total costs* *costs reported as an outcome*	
Study design	*Cost utility* *Cost effectiveness* *Cost consequence* *Cost/resource use*	*Studies with only clinical outcomes*
Publication type	*Primary paper*	*Published before March 2013*

	Abstract *HTA review* *Systematic review* *Published from March 2013 to April 2014*	*Editorial* *Review* *Letter* *Reference included in original systematic review*
Language restrictions	*English*	*Non-English languages*

ASCT, autologous stem cell transplantation; CUA, cost–utility analysis; HTA, health technology assessment; ICER, incremental cost effectiveness ratio; LYG, life-years gained; MM, multiple myeloma; QALY, quality-adjusted life-year; rr, relapsed/refractory.

Source: Submission Table 37

The ERG is content with the searches for this element of the submission.

5.1.1.2. Search results

The ERG are concerned as no PRISMA (preferred reporting items for systematic reviews and meta-analysis) is presented for cost-effectiveness searches; it is not possible to tell how many studies were identified through searches or excluded.

Novartis state their systematic review identified 14 cost-utility studies, however only seven studies were reviewed in detail in full papers or HTA submissions and were presented (Table 37). No description of these studies is presented by the company. The ERG summarise these studies only in the table (see below). In addition, Novartis state that construction of the economic model was informed by the review of the previous modelling approaches. The ERG was not clear whether Novartis was referring to separate searches or these seven studies were identified by the systematic review mentioned above. However, when the ERG reviewed the Appendix 17 of the submission where the subgroup analysis is performed, the ERG found that a targeted literature search was performed to identify previously published parhmacoeconomic models and HTA submissions. The ERG assume that Novartis was referring to the targeted literature review, however, it is not clear from the submission.

Furthermore, in the table below there are footnotes for NICE HTA 2009[75] ICER column, but no data is presented.

Table 37: Summary list of other cost-effectiveness evaluations

Study	*Year*	*Country(ies) where study was performed*	*Summary of model*	*QALYs (intervention, comparator)*	*Costs (currency) (intervention, comparator)*	*ICER (per QALY gained)*
HTA 2007[76] (Green et al, 2009[77])	*2007*	*England and Wales*	*Semi-Markov state transition*	*NR*	*NR*	*BTZ versus HiDEX: £38,000*

[75] National Institute for Health and Care Excellence. Technology Appraisal 171: Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. June 2009. Available from: http://www.nice.org.uk/TA171. (Accessed 4 October 2013).

Study	Year	Country(ies) where study was performed	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			model			
Hornberger et al, 2010[78]	2010	Sweden	Partitioned survival model	BTZ versus HiDEX: 0.04 BTZ versus LEN/DEX: 0.69	BTZ versus HiDEX: SEK 902,874 BTZ versus LEN/DEX: cost-saving	BTZ versus HiDEX: SEK 662,621 BTZ versus LEN/DEX: dominant
Moller et al, 2011[79]	2011	Norway	Discrete event simulation model	LEN/DEX versus BTZ: 0.76	LEN/DEX versus BTZ: NOK188,245	LEN/DEX versus BTZ: NOK247,048
NICE HTA 2009[80]	2009	England and Wales	Partitioned survival model	LEN/DEX versus BTZ (if 1 prior therapy): NR LEN/DEX versus DEX (if ≥ 2 prior therapies): 1.86 LEN/DEX versus DEX (if 1 prior therapy, THAL): 1.7	LEN/DEX versus BTZ (if 1 prior therapy): NR LEN/DEX versus DEX (if ≥ 2 prior therapies): NR LEN/DEX versus DEX (if 1 prior therapy, THAL): NR	LEN/DEX versus BTZ (if 1 prior therapy): £46,865 LEN/DEX versus DEX (if ≥ 2 prior therapies): £30,350[b] LEN/DEX versus DEX (if 1 prior therapy, THAL): £28,941[b]
Brown et al, 2013[81]	2013	England and Wales	Individual simulation	LEN/DEX versus	LEN/DEX versus	LEN/DEX versus

[76] National Institute for Health and Care Excellence. Technology Appraisal 129: Bortezomib monotherapy for relapsed multiple myeloma. October 2007. Available from: www.nice.org.uk/TA129 (Accessed 4 October 2013).

[77] Green C, Bryant J, Takeda A et al. Bortezomib for the treatment of multiple myeloma patients. Health Technol Assess 2009;13 (Suppl 1):29–33.

[78] Hornberger J, Rickert J, Dhawan R et al. The cost-effectiveness of bortezomib in relapsed/refractory multiple myeloma: Swedish perspective. Eur J Haematol 2010;85 484–91.

[79] Moller J, Nicklasson L, Murthy A. Cost-effectiveness of novel relapsed-refractory multiple myeloma therapies in Norway: lenalidomide plus dexamethasone vs bortezomib. J Med Econ 2011;14 690–7.

[80] National Institute for Health and Care Excellence. Technology Appraisal 171: Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. June 2009. Available from: http://www.nice.org.uk/TA171. (Accessed 4 October 2013).

Study	Year	Country(ies) where study was performed	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			model	DEX in patients who have received 1 prior therapy: 2.2	DEX in patients who have received 1 prior therapy: £66,483	DEX in patients who have received 1 prior therapy: £30,153
Fragoulakis et al, 2013[82]	2013	Greece	Discrete event simulation model	LEN/DEX versus BTZ: 0.79	LEN/DEX versus BTZ: €30,402	LEN/DEX versus BTZ: €38,268
NICE HTA 2014[83]	2014	England and Wales	Partitioned survival model	POM/LoDEX versus BTZ/DEX : 0.61 POM/LoDEX versus CTD: 0.61 POM/LoDEX versus BTD: 0.61	POM/LoDEX versus BTZ/DEX :£30,782 POM/LoDEX versus CTD: £47,219 POM/LoDEX versus BTD: £44,142	POM/LoDEX versus BTZ/DEX : £50,366 POM/LoDEX versus CTD: £77,915 POM/LoDEX versus BTD: £72,250

BTD, bendamustine plus thalidomide and dexamethasone; BTZ, bortezomib; CTD, cyclophosphamide plus thalidomide and dexamethasone; DEX, dexamethasone; HiDEX, high dose dexamethasone; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LoDEX, low dose dexamethasone; NICE, National Institute for Health and Care Excellence; NR, not reported; POM, pomalidomide; QALY(s), quality-adjusted life year(s); THAL, thalidomide.

Source: Submission Table 38

The company only presented the table with the summary of 7 studies. It is not clear to the ERG why the rest 7 studies were omitted from the submission. Below the ERG present a short summary of the studies presented in the table above.

HTA 2007[84] is a technology appraisal guidance for use of BTZ monotherapy for relapsed multiple myeloma. This guidance recommends use of BTZ monotherapy in patients with MM who have relapsed for the first time after having one prior treatment and who had a bone marrow transplant (unless unsuitable for transplantation). This TA guidance states that treatment should be only continued if there is at least a partial response after 4 cycles.

[81] Brown RE, Stern S, Dhanasiri S, Schey S. Lenalidomide for multiple myeloma: cost-effectiveness in patients with one prior therapy in England and Wales. Eur J Health Econ 2013;14 507–14.

[82] Fragoulakis V, Kastritis E, Psaltopoulou T, Maniadakis N. Economic evaluation of therapies for patients suffering from relapsed-refractory multiple myeloma in Greece. Cancer Manag Res 2013;5 37–48.

[83] Celgene. NICE Single Technology Appraisal (STA) - Pomalidomide for relapsed and refractory multiple myeloma. June 2014.

[84] National Institute for Health and Care Excellence. Technology Appraisal 129: Bortezomib monotherapy for relapsed multiple myeloma. October 2007. Available from: www.nice.org.uk/TA129 (Accessed 4 October 2013).

Green et al, 2009[85] present a clinical effectiveness and economic analysis of BTZ in comparison with high dose DEX for use in patient with MM at first relapse or beyond. The study found that the estimated cost per LY gained was £30,750. A various sensitivity analyses were also performed.

Hornberger et al, 2010[86] estimate the cost-effectiveness of BTZ in comparison with DEX and LEN/DEX for treatment of relapsed/refractory MM for Swedish perspective. A partitioned survival analysis model was used and concluded that both BTZ and LEN/DEX are estimated to prolong survival in comparison to DEX. The study found that BTZ was cost-effective from Swedish perspective in comparison with DEX and the mean incremental cost per QALY of BTZ in comparison with DEX was 2010 SEK 902,874 (€95 073) and "was dominant with respect to LEN/DEX".

Moller et al, 2011[87]using a discrete simulation model the cost-effectives analysis of LEN/DEX in comparison to BTZ for the treatment of relapsed-refractory multiple myeloma in Norway was conducted. The study found that LYs and QALYs were higher for LEN/DEX in comparison with BTZ. Compared with BTZ, he incremental cost per QALY gained from LEN/DEX therapy was NOK 247,978; the incremental cost per LY gained was NOK 198,714.

NICE HTA 2009[88] is a technology appraisal guidance for use of LEN therapy for relapsed multiple myeloma in patients who have received at least one prior therapy. LEN in combination with DEX is recommended a possible treatment option as the 3rd line on later treatment. People who receive this treatment take their medication until they and their healthcare professionals decide to stop the treatment.

Using an individual simulation model, Brown et al, 2013[89] conducted a cost-effectiveness analysis of LEN/DEX in comparison with DEX monotherapy in patients with multiple myeloma who have failed one prior therapy. The model estimated an improvement in time to progression of 9.5 months, increased life years (3.2) and QALYs gained (2.2). The ICER per QALY gained was estimated at £30,153.

Using a discrete event simulation method Fragoulakis et al, 2013[90] aimed to estimate the cost-effectiveness of LEN/DEX in comparison with BTZ monotherapy from Greek perspective. The incremental QALY gain for the LEN/DEX therapy was 0.79. The incremental cost per LY was estimated at €29,415 and the incremental cost per QALY was calculated at €38,268. Fragoulakis and colleagues state

[85] Green C, Bryant J, Takeda A et al. Bortezomib for the treatment of multiple myeloma patients. Health Technol Assess 2009;13 (Suppl 1):29–33.

[86] Hornberger J, Rickert J, Dhawan R et al. The cost-effectiveness of bortezomib in relapsed/refractory multiple myeloma: Swedish perspective. Eur J Haematol 2010;85 484–91.

[87] Moller J, Nicklasson L, Murthy A. Cost-effectiveness of novel relapsed-refractory multiple myeloma therapies in Norway: lenalidomide plus dexamethasone vs bortezomib. J Med Econ 2011;14 690–7.

[88] National Institute for Health and Care Excellence. Technology Appraisal 171: Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. June 2009. Available from: http://www.nice.org.uk/TA171. (Accessed 4 October 2013).

[89] Brown RE, Stern S, Dhanasiri S, Schey S. Lenalidomide for multiple myeloma: cost-effectiveness in patients with one prior therapy in England and Wales. Eur J Health Econ 2013;14 507–14.

[90] Fragoulakis V, Kastritis E, Psaltopoulou T, Maniadakis N. Economic evaluation of therapies for patients suffering from relapsed-refractory multiple myeloma in Greece. Cancer Manag Res 2013;5 37–48.

that "The probability of lenalidomide–dexamethasone being a cost-effective therapy option at a threshold three times the per capita income (€60,000 per QALY) was higher than 95%".

The 7th cited reference, NICE HTA 2014[91] is Celgene submission for use of pomalidomide for treatment of relapsed and refractory multiple myeloma in patients who had received at least 2 prior lines of treatment including LEN and BTZ. The cost-effectiveness results of this study are presented in Table 37. The publicaition date of the appraisal is yet to be confirmed[92].

Novartis refer the reader to Appendix 12 for the quality assessment of the cost-effectiveness studies. There are some uncertainties around the quality assessment of the studies. First, it seems that quality assessment was performed for six studies in total: three abstracts and three full papers. The three abstracts were:

- Schey 20126[93];
- Jiang 2011[94];
- Walker 2011[95].

These three papers are not included in the summary of "*other cost-effectiveness evaluation"* **Table 37**. The ERG assumes that these three papers have been excluded; however, if the company identified 14 studies, there is still a lack of quality assessment for four studies that have been excluded.

Quality assessment is also performed for three other studies that are included in "*other cost-effectiveness evaluation"* **Table 37**:

- HTA LEN/DEX 2009[96];
- HTA BTZ 2007[97] and Green et al. 2009[98];

[91] Celgene. NICE Single Technology Appraisal (STA) - Pomalidomide for relapsed and refractory multiple myeloma. June 2014.

[92] NICE. 2014. Relevance to NICE guidance programmes. Available from https://www.nice.org.uk/advice/esnm32/chapter/Relevance-to-NICE-guidance-programmes (Acessed 24/07/2015).

[93] Schey S, Stern S, Dhanasiri S, Brown R. Cost-effectiveness if lenalidomide/dexamethasone in multiple-myeloma patients with prior thalidomide therapy. Haematologica 2012;97 (Suppl 1):1087.

[94] Jiang Y, Spencer M, Gauthier A, Pacou M. A cost-effectiveness analysis for second-line treatment of relapsed/refractory (RR) multiple myeloma (MM) in the United Kingdom. Value Health 2011;14:A452

[95] Walker SA, Izmirlieva MA, Mehta P. A cross-country comparison of second-line multiple myeloma treatments. Value Health 2011;14:A175.

[96] National Institute for Health and Care Excellence. Technology Appraisal 171: Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. June 2009. Available from: http://www.nice.org.uk/TA171. (Accessed 4 October 2013).

[97] National Institute for Health and Care Excellence. Technology Appraisal 129: Bortezomib monotherapy for relapsed multiple myeloma. October 2007. Available at: www.nice.org.uk/TA129. (Accessed 4 October 2013)

[98] Green C, Bryant J, Takeda A et al. Bortezomib for the treatment of multiple myeloma patients. Health Technol Assess 2009;13 (Suppl 1):29–33.

- Brown et al. 2013[99].

Again, the ERG is not clear why quality assessment was performed for three studies only. Though, technically, the cited NICE HTA 2014[100] is a submission of Celgene to NICE. Quality assessment of the four studies listed below is not included in the submission:

- Hornberger et al, 2010[101];
- Moller et al, 2011[102];
- Fragoulakis et al, 2013[103];
- NICE HTA 2014[104].

In summary, there are a number of issues with the presented evidence:

- It is not clear how many studies have been identified in the search;
- Novartis do not state why seven studies out of 14 were excluded. The company do not provide the study list either. It is only by looking in the Appendix 12 for the quality assessment when the reader discovers three studies that were excluded;
- Novartis only present quality assessment for 6 studies out of 14.

5.1.2. Novartis' economic model submitted to NICE

We now turn to the economic evaluation that Novartis presented to NICE. Novartis report cost per QALY estimates for PANO/BTZ/DEX vs. BTZ/DEX for the full cohort included in the PANORAMA-1 trial which enrolled patients with relapsed or relapsed and refractory MM who had received one to three previous treatments.

The model was built in Microsoft Excel©. Here, we summarise the main features of the model.

5.1.2.1. Model structure

Novartis developed a decision analytic semi-Markov model. The structure of the model, illustrated in Figure 23, includes two pre-progression health states, two post-progression health states and finally the death health state. The model is reported to capture the three key aspects of MM that are affected by disease progression and the effects of treatment, namely survival, HRQL and costs.

[99] Brown RE, Stern S, Dhanasiri S, Schey S. Lenalidomide for multiple myeloma: cost-effectiveness in patients with one prior therapy in England and Wales. Eur J Health Econ 2013;14 507–14.

[100] Celgene. NICE Single Technology Appraisal (STA) - Pomalidomide for relapsed and refractory multiple myeloma. June 2014.

[101] Hornberger J, Rickert J, Dhawan R et al. The cost-effectiveness of bortezomib in relapsed/refractory multiple myeloma: Swedish perspective. Eur J Haematol 2010;85 484–91.

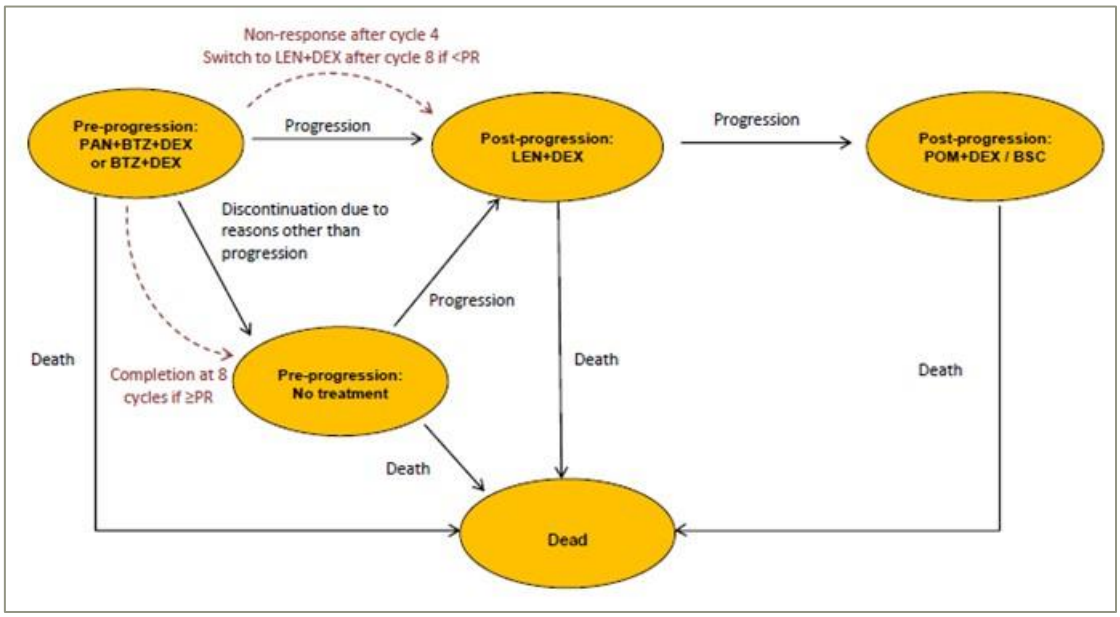
[102] Moller J, Nicklasson L, Murthy A. Cost-effectiveness of novel relapsed-refractory multiple myeloma therapies in Norway: lenalidomide plus dexamethasone vs bortezomib. J Med Econ 2011;14 690–7.

[103] Fragoulakis V, Kastritis E, Psaltopoulou T, Maniadakis N. Economic evaluation of therapies for patients suffering from relapsed-refractory multiple myeloma in Greece. Cancer Manag Res 2013;5 37–48.

[104] Celgene. NICE Single Technology Appraisal (STA) - Pomalidomide for relapsed and refractory multiple myeloma. June 2014.

Even if the model consists of three key health states, it describes five health states:
Health state A: pre-progression, on treatment;
Health state B: pre-progression, off treatment;
Health state C: post-progression, LEN/DEX as third line therapy;
Health state D: post-progression, POM/DEX or other active treatments and/or supportive care as LLoT.

Figure 23: Structure of the model



Source: Submission Figure 37

All patients enter the model in the pre-progression health state A and receive either PANO/BTZ/DEX or BTZ/DEX. Patients progress by moving from the two pre-progression health states, A and B, to the post-progression health state C (LEN/DEX) and then D corresponding to fourth-line therapy (POM/DEX together with supportive care).

Patients in the PANO/BTZ/DEX treatment arm discontinue early due to progression or relapse and move to C, or discontinue due to reasons other than progression and move to B. Patients who discontinue treatment due to progression or relapse or have not achieved a PR will move to C, while those who discontinue due to reasons other than progression and have at least a PR stop treatment and remain off treatment in B, until they experience progression and move to C. Following progression, patients will move to D until death.

The treatment pathway is similar for patients in the BTZ/DEX arm for the first four cycles. In order to reflect the BTZ label, patients are then evaluated for response and will continue on BTZ/DEX only if they achieve at least a PR, otherwise they move to C. Patients who are in health state B at the end of cycle 4 are not subjected to response evaluation. To reflect UK clinical practice, the company have

implemented another stopping rule at the end of cycle 8 so that 90% of the patients still on BTZ/DEX treatment would stop treatment. The remaining 10% are allowed to continue BTZ/DEX until progression or discontinuation for other reasons up to 16 cycles as per the PANORAMA-1 protocol. Patients in health state B with at least a PR will remain there until disease progression while the others will move to C. Thereafter patients progress to health state D to received LLoT until death.

Patients are at risk of dying at any time therefore they can move to that health state from any other health state.

The efficacy data that is used for the control arm is based on the PANORAMA-1 trial that did not require patients to discontinue therapy.

The cycle length in the economic model is three weeks to reflect the drug administration schedule in PANORMA-1 trial and a half-cycle correction was applied.

The time horizon considered in the economic model was 25 years.

5.1.2.2. Treatment effectiveness within submission

Treatment effectiveness within the model works essentially through transition probabilities between the health states presented in the previous section. The transition probabilities were derived from survival functions based primarily on patient-level data from the PANORAMA-1 trial.

The **Table 38** below reproduced from the submission summarises the approaches used to derived transition probabilities and their use in the model.

Table 38: Approaches used to derived transition probabilities and their use in the economic model

Parameter	Data source	Model used for base case	Use of transition probabilities
PANO/BTZ/DEX			
Risk of progression or death	PANORAMA-1, PANO/BTZ/DEX Patient-level PFS data	Weibull	Health State A, PANO/BTZ/DEX
Risk of progression (and risk of death)	PANORAMA-1, PANO/BTZ/DEX Patient-level PFS data	Logistic regression with treatment indicator and the log of cycle	Health State A, PANO/BTZ/DEX
Risk of treatment discontinuation	PANORAMA-1, PANO/BTZ/DEX Patient-level data for PFS and treatment exposure	Log-logistic	Health State A, PANO/BTZ/DEX
BTZ/DEX, cycles 1 to 4			
Risk of progression or death	PANORAMA-1 BTZ/DEX Patient-level PFS data	Weibull	Health State A, BTZ/DEX cycles 1 to 4
Risk of progression (and risk of death)	PANORAMA-1 BTZ/DEX Patient-level PFS data	Logistic regression with treatment indicator and the log of cycle	Health State A, BTZ/DEX cycles 1 to 4
Risk of treatment discontinuation	PANORAMA-1, BTZ/DEX Patient-level data for PFS and treatment exposure	Log-logistic	Health State A, BTZ/DEX cycles 1 to 4
BTZ/DEX responders, cycles 5 to 8			
Risk of progression or death	PANORAMA-1 BTZ/DEX responders Patient-level PFS data	Weibull	Health State A, BTZ/DEX cycles 1 to 4
Risk of progression (and risk of death)	PANORAMA-1 BTZ/DEX responders Patient-level PFS data	Logistic regression with treatment indicator and the log of cycle	Health State A, BTZ/DEX cycles 1 to 4
Risk of treatment discontinuation	PANORAMA-1, BTZ/DEX responders Patient-level data for PFS and treatment exposure	Exponential	Health State A, BTZ/DEX cycles 1 to 4
BTZ/DEX, discontinuing treatment during cycles 1 to 4 without disease progression			
Risk of progression	PANORAMA-1 BTZ/DEX discontinuers before cycle 4, patient level data for TTP	Exponential[a]	Health State A. BTZ/DEX cycles 5 to 8

Risk of death	PANORAMA-1 BTZ/DEX dicontinuers before cycle 4, patient level data for OS	Exponential[a]	Health State A. BTZ/DEX cycles 5 to 8
BTZ/DEX discontinuing treatment during cycles 5 to 8 without disease progression			
Risk of progression	PANORAMA-1 BTZ/DEX dicontinuers between cycles 5 to 8, patient level data for TTP	Exponential[a]	Health State B. BTZ/DEX cycle 9 onwards
Risk of death	PANORAMA-1 BTZ/DEX dicontinuers between cycles 5 to 8, patient level data for OS	Exponential[a]	Health State B. BTZ/DEX cycle 9 onwards
LEN/DEX			
Risk of progression	Median TTP estimate from the combined MM-009/010 trials	Exponential[a]	Health State C, LEN/DEX
Risk of death	PANORAMA-1 Patient-level OS data for patients who received LEN/DEX after trial regimen, stratified according to whether patients progressed within first 4 cycles or later	Exponential[a]	Health State C, LEN/DEX
Last line of treatment			
Risk of death	PANORAMA-1 Patient-level OS data for patients who received LEN/DEX after trial regimen, stratified according to whether patients progressed within first 4 cycles or later	Exponential[a]	Health State D, LLoT

[a]Chosen to keep model parsimonious

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; LLoT, last line of treatment; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; TTP, time to progression.

Dimopoulos et al 2009[105]

Source : Submission Table 40

[105] Dimopoulos MA, Chen C, Spencer A et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia 2009;23:2147–52

The key data on which the economic modelling is based is that on progression free survival (PFS). In a first step, parametric survival models (exponential, Weibull, log-logistic, log-normal and Gompertz) were fitted on Kaplan-Meier plots of PFS data in order to provide an estimate of the risk of progression or death in a given cycle. However, as patients are both at risk of progressing to the next treatment and death, the proportion of patients who progressed relative to those who had a PFS event (death or disease progression) was estimated for each cycle by a logistic regression in a second step. Thus, from the set of individuals that are either currently receiving treatment or have had treatment discontinued, a logistic regression model is used simultaneously to determine the proportion of those that will either die or progress. The submission notes that individuals who have previously discontinued treatment can suddenly progress during a cycle – hence a separate conditional logistic regression model is used.

In the model, the probability of a PFS event per cycle is calculated using the model described on the excel model sheet P(PFS). The impact of progression-free survival on the passage of patients through the model is shown in the column labelled 'LEN+DEX, PrePD'. PrePD appears to imply pre-progression death because it includes those who progress to LEN+DEX treatment plus those who die currently on PAN+BTX+DEX treatment or those who die whilst off treatment (discontinued). In the model, the death health state does not appear to be a well-defined stage but in the Markovian terminology it can be thought of as an absorbing state since those who enter it effectively leave the model.

The proportion of individuals moving to stage C, shown in column LEN+DEX, is therefore only a proportion of this group since it also includes those who have died during the cycle from stages A and B. Again a logistic model is used and described on the P(prog) sheet of the excel model. Finally the column PrePD is defined as the proportion of individuals that die either from stage A or B and is calculated by considering the difference between the progressed patients and those that died minus only those who progressed. Consequently columns J through Q on the Markov PAN+BTZ+DEX sheet in appear to explain the movements from stages A and B to both death and stage C.

The number of individuals off treatment (stage B) at the end of a period is calculated using the proportion of people who started in either stage A or stage B as these are the only source of individuals for stage B. However this number has to be adjusted by the number who progressed during the period, in this case to stage C, or died during the period whilst in stages A or B. Because some of the people that began in stage A will remain in stage A at the end of the period this number is corrected by the number of people remaining in A at the end of the cycle.

As data on progression in patients receiving antineoplastic treatment after PANO/BTZ/DEX or BTZ/DEX was not collected in the PANORAMA-1 trial, it is stated in section 5.3.3 of the submission that the risk of progression or death on LEN/DEX (or leaving the LEN/DEX health state) was based on published data from the pooled MM-009 and -010 studies. The risk of progression on LEN/DEX and the risk of post-progression death were assumed to be the same for both PANO/BTZ/DEX and BTZ/DEX groups. The risk of post-progression (LEN/DEX and subsequent LLoT) death is based on patient-level post-progression OS data from PANORAMA-1 for patients receiving LEN/DEX as a subsequent antineoplastic treatment after PANO/BTZ/DEX or BTZ/DEX.

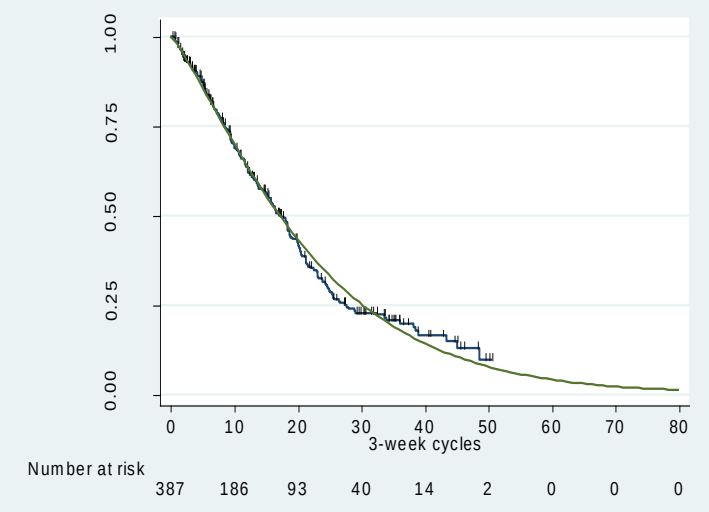
Clinical input parameters were derived using a similar approach in both PANO/BTZ/DEX and BTZ/DEX groups except that, in BTZ/DEX patients, parameters were obtained separately for cycles 1 to 4 and cycles 5 to 8. Parameters for cycles 1 to 4 were derived using patient-level data from the overall population receiving BTX/DEX in PANORAMA-1 while parameters for cycles 5 to 8 and subsequent

cycles are drawn from patient-level data for responding patients. This reflects the modelling assumption that only patients achieving at least a PR continue to receive BTZ/DEX at cycles 5 to 8 or beyond. The model uses 55.12% as the probability that a patient achieved response by the end of cycle 4. This figure was taken from the Kaplan-Meier estimates.

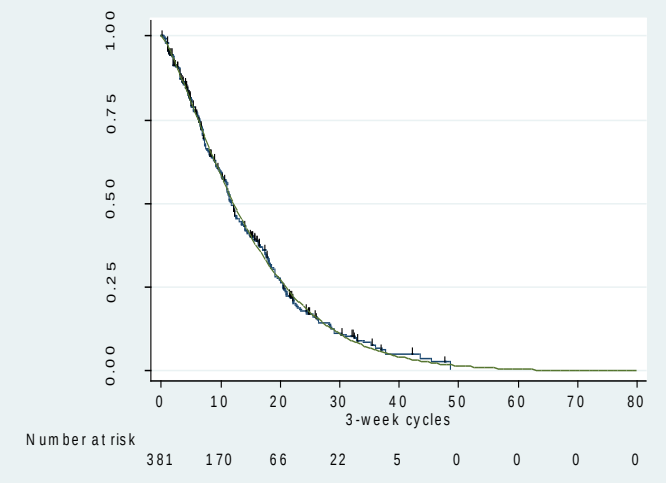
On the basis of Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) assessments and visual inspection, the Weibull model was the preferred means of modelling PFS data in the full analysis set, while the log-logistic model was considered to provide the best representation of discontinuation while on PANO/BTZ/DEX and BTZ/DEX (all patients). The exponential model was selected in the base case for PFS modelling of BTZ/DEX responders; it is feasible that a different model could be appropriate for this group as responders will be qualitatively different from, non-responders. The models that they have used can be found on the excel model sheet P(prog). Figure 24 was taken from the original submission and it shows the Kaplan-Meier PFS curves as well as the fitted PFS curves

Figure 24: Kaplan–Meier curve and fitted Weibull model for PFS: full analysis set from PANORAMA-1 trial, a) PANO/BTZ/DEX, b) BTZ/DEX all patients, c) BTZ/DEX responders

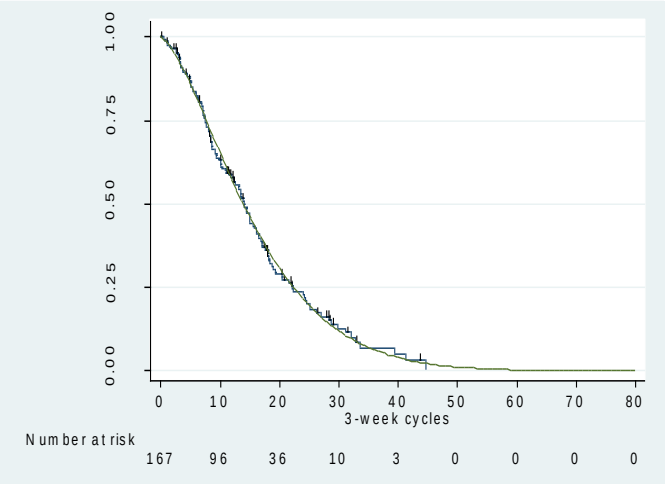
a) **PANO/BTZ/DEX**



b) BTZ/DEX all patients



c) BTZ/DEX responders

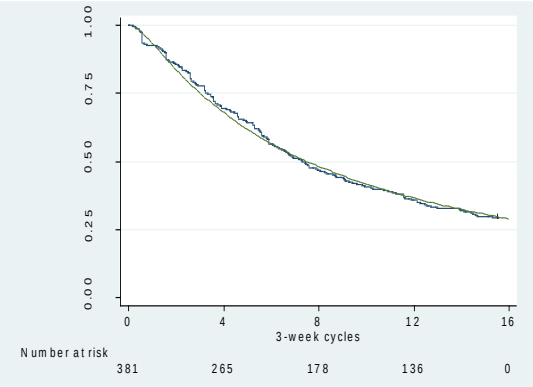


BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; PFS, progression-free survival.
Source: Submission Figure 38

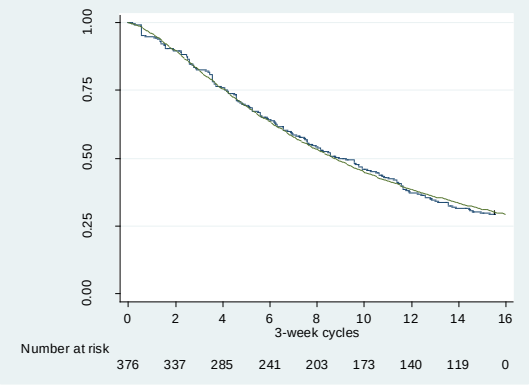
The transition probabilities for risk of treatment discontinuation were derived in the same way as for the risk of progression or death. The same five parametric survival models were fitted to treatment discontinuation data from the PANORAMA-1 trial using the safety analysis set of patients received at least one dose of study treatment. This consisted of 381 PANO/BTZ/DEX and 377 BTZ/DEX patients compared with 387 and 381 patients in the full analysis set. Subsequently, AIC and BIC values are provided to justify the use of the log-logistic distribution to be the best fitting model amongst the five tested for discontinuation while on PANO/BTZ/DEX and BTZ/DEX (full safety set). The exponential model was considered the best model for BTZ/DEX responders. The Kaplan-Meier plots and fitted models are reported in
Figure **25** below.

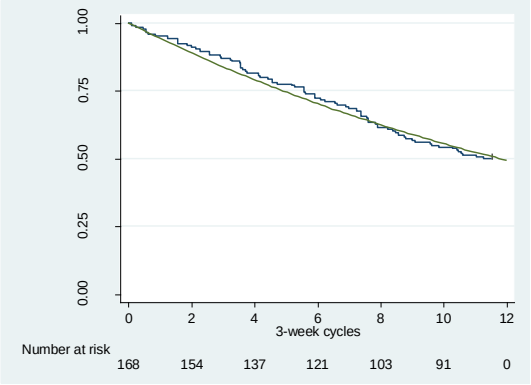
Figure 25: Kaplan–Meier curve and fitted log-logistic model (a and b) or exponential model (for c) for the proportion of patients without treatment discontinuation: full safety set from PANORAMA-1 trial, a) PANO/BTZ/DEX, b) BTZ/DEX all patients, c) BTZ/DEX responders

a) PANO/BTZ/DEX



b) BTZ/DEX all patients,





c) BTZ/DEX responders

Source: Submission Figure 40

All patients start by receiving treatment in stage A. At the first cycle, some of those patients will stop receiving treatment: this is known as discontinuation in the model. In the PANO/BTZ/DEX group, discontinuation is estimated with a log-logistic regression model fitted to the original dataset of those already on treatment in order to identify those who will discontinue treatment or not. The model derives the probability of discontinuation (moving to stage B from A) as a function of the time spent on treatment without progression (i.e. the natural logarithm of cycle length). The submission states that the log-logistic distribution was judged to be the best model for discontinuation in those receiving PANO/BTZ/DEX and BTZ/DEX (all patients). However, in the model, the distribution used to model discontinuation in BTZ/DEX patients is labelled 'logistic regression'. A logistic model is appropriate since

it predicts the outcome as a binary variable and hence there are two possible outcomes (discontinue treatment or not) and allows to non-monotonic hazards.

With respect to BTZ responders at cycle 5, the only individuals on BTZ are the ones who have had a positive response to the treatment. Those who have had a less than a PR in the period between the start of cycle 4 and 5 are switched to LEN+DEX and thus no positive responders to the treatment in cycle 5 begin having had their treatment discontinued. The estimated exponential distribution of time to disease progression applies only to those that responded thus the time used by the fitted distribution is shifted to the right by 4 cycles. Thus the 1st period in which the patient has a positive response relates to cycle 5 in the model.

For patients discontinuing BTZ/DEX during cycles 1 to 4 and who did not experience progression until the end of cycle 4, the probabilities of progression and death were estimated by fitting exponential survival curves to Kaplan–Meier plots for TTP and OS. A similar procedure was implemented for patients who are off-treatment at the end of cycle 8 because they discontinued treatment between cycles 5 and 8 but did not experience progression during this period. For cycles 1 to 4 and 5 to 8, the exponential model was considered a sufficiently good fit for TTP and OS data in the two relatively small samples of patients (18 at cycles 1 to 4 and 14 at cycles 5 to 8) on the basis of visual inspection. On the same basis, the exponential distribution was chosen to model the risk of progression on LEN/DEX and the risk of post-progression death on LEN/DEX and subsequent LLoT.

5.1.2.3. Health related quality of life

Patient-reported assessments of HRQL, disease symptoms and treatment-related AEs were obtained from EORTC QLQ-C30 and EORTC-MY20 questionnaires administered at screening and before study drug treatment on cycle 1 day 1 and every six weeks subsequently. Since neither EORTC measure can be used as the basis for QALYs, a mapping approach was used to derive utilities. A search of PubMed and the University of Oxford Health Economics Research Centre (HERC) mapping database found four references relating to the mapping of either EORTC measure to EQ-5D for patients with MM. One study more closely reflected the patient population enrolled into the PANORAMA-1 trial than the others identified as it was based on patients with MM of whom around 50% had received more than one prior treatment. This study used multiple linear regression techniques to obtain algorithms mapping from both questionnaires to EQ-5D and from QLQ-C30 alone to EQ-5D. Since both models had similar explanatory power, the model mapping QLQ-C30 to EQ-5D was adopted to allow as much data as possible from the PANORAMA-1 study to be used.

In section 5.4.2, the submission states that the *"mapped utility values were lower for PANO/BTZ/DEX than for BTZ/DEX at all time points*". This was noted to be consistent with the higher incidence of AEs in PANO/BTZ/DEX compared to BTZ/DEX treatment (section 5.4.4). Overall mean utility values are reported to be 0.706 and 0.725 in PANO/BTZ/DEX and BTZ/DEX groups, respectively. These values were used for the 'pre-progression, on treatment' states, A. A lower value of 0.64 was obtained from the literature for the two post-progression states (C and D: third-line therapy and LLoT) as no HRQL data was available from PANORAMA-1 for the post-progression health states. In the absence of HRQL data from PANORAMA-1 in patients who discontinued treatment or after completion of treatment and before disease progression, the utility of the 'pre-progression, no treatment' health state, B, was assumed to be equal to the mean utility mapped from the last HRQL assessment while still on treatment and was based on pooled data from both treatment groups. Therefore the pre-progression, no treatment health state was associated with a utility of 0.762. A higher utility in this health state is consistent with evidence from the literature indicating that, prior to stopping therapy, HRQL improves

when patients come off treatment compared with when they are on treatment. Utility values used in the model are presented in the table below.

Table 39: Utility values by state

Health state	*Utility (SD) n = 4172*[a]
A: Pre-progression, PANO/BTZ/DEX	*0.706 (0.192)*
A : Pre-progression, BTZ/DEX	*0.725 (0.197)*
B: Pre-progression, No treatment	*0.762 (0.166)*
C and D: Post-progression, LEN/DEX and Post-progression, LLoT	*0.64 (0.129)*[b]
Dead	*0*

[a] Number of HRQL measurements, 2031 and 2141 on PANO/BTZ/DEX and BTZ/DEX arms, respectively; [b]Standard error, assumed to be 20% of the mean value.
BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; LLoT, last line of treatment; PANO, panobinostat; SD, standard deviation.
Source: Submission Table 49

5.1.2.4. AEs

No search was conducted for evidence on AEs.

Novartis estimated the occurrence of AE associated with the two treatment arms based on the AEs reported in PANORAMA-1. Although HRQL utility values were derived form QLQ-C30 trial outcomes, which may have captured some of the AEs differences between arms, the AE utility decrements were not included in the cost-effectiveness analysis. Novartis do not provide a justification for this.

Management cost of the ten most frequently occurring grade 3 / 4 AEs were applied to patients in pre-progression state (receiving PANO/BTZ/DEX or BTZ/DEX). Novartis claim that the 3-weekly probabilities of AEs were estimated from the number of patients receiving PANO/BTZ/DEX or BTZ/DEX who experienced a grade 3 / 4 AEs in patients in PANORAMA-1.

Novartis present the table of AEs as observed in the PANORAMA-1 trial population. Daily AE rates for patients receiving PANO/BTZ/DEX or BTZ/DEX were converted into 3-weekly occurrence rates and then transformed into 3-weekly probabilities.

The ERG note that number of patients with Lymphopenia is different in the model. In the model, a number of patients with Lymphopenia in PANO/BTZ/DEX is 47 and in BTZ/DEX, a number of patients with Lymphopenia is 28 in contrast to 35 and 12 respectively as presented in the table 59 in the submission. In addition, the ERG note that the 3-weekly occurrence probability of grade ¾ AEs is in disagreement with the model inputs. The updated table with the actual values upon which the model results are based is presented below.

Table 40: AEs as observed in the full PANORAMA-1 trial population (safety set)

	PANO/BTZ/DEX (n = 381)		BTZ/DEX (n = 377)	
Mean study treatment exposure, days	*183.5*		*195.0*	
Total exposure time to treatment, patient-days	*69,913.5*		*73,515*	
Grade 3 / 4 AEs	*N*	*3-weekly occurrence probability*	*N*	*3-weekly occurrence probability*
Anaemia	*63*	***0.019***	*60*	***0.017***
Asthenia	*36*	***0.011***	*14*	***0.004***
Diarrhoea	*97*	***0.029***	*30*	***0.009***
Fatigue	*65*	***0.019***	*33*	***0.009***
Hypokalaemia	*73*	***0.022***	*24*	***0.007***
Hyponatraemia	*37*	***0.011***	*13*	***0.004***
Lymphopenia	***47***	***0.014***	***28***	***0.008***
Neutropenia	*92*	***0.027***	*30*	***0.009***
Pneumonia	*48*	***0.014***	*39*	***0.011***
Thrombocytopenia	*217*	***0.063***	*94*	***0.026***

AEs, adverse events; BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat; N, number of patients with AE.

Source: Adapted from the submission Table 59

Monitoring costs were derived from a number of sources and only direct cost were taken into account. These costs were not applied to 3rd or 4th line of treatment.

The table with cost per AE is presented below.

Table 41: Costs per AE

Grade 3 and 4 adverse events	*Unit cost*	*Source*
Anaemia	*£1,155*	*2014, Non-Elective Inpatients – Long Stay, Iron Deficiency Anaemia (SA04L), National schedule of reference costs (2013-2014)*
Asthenia	*£12*	*2013, TA316*
Diarrhoea	*£623*	*2013, TA316*
Fatigue	*£12*	*2013, TA316*
Hypokalaemia	*£355*	*2014, High Cost Drugs, Intravenous Nutrition, Band 1 (XD26Z), National schedule of reference costs (2013–2014)*
Hyponatraemia	*£355*	*Assumed to be the same as Hypokalaemia*
Lymphopenia	*£167*	*Assumed to be the same as Neutropenia*
Neutropenia	*£167*	*2014, High Cost Drugs, Neutropenia Drugs, Band 1 (XD25Z), National schedule of reference costs (2013–2014)*
Pneumonia	*£1,433*	*2014, Non-Elective Inpatients – Long Stay, Atypical or Viral Pneumonia (DZ11J), National schedule of reference costs (2013–2014)*
Thrombocytopenia	*£604*	*2013, Non-Elective Inpatients – Short Stay, Thrombocytopenia (SA12K), National schedule of reference costs (2013–2014)*

Source: Submission Table 60

As a result, the cost of management of AEs per cycle was estimated at £117 for PANO/BTZ/DEX and £63 for BTZ/DEX. This cost was applied to each cycle of treatment for patients in the Health state A (pre-progression on treatment).

5.1.2.5. Resources and costs

The model submitted by Novartis used costs based on the NHS & Personal Social Services (PSS) perspective. Novartis clarified that PSS perspective was considered but no particular aspects were identified for inclusion. Costs included in the model are drug costs and disease management costs (such as monitoring costs, administration costs and outpatient visits) and AE costs.

AEs were costed using NHS reference costs and Technology Appraisals and these are addressed in section **Error! Reference source not found.** of this report. Other miscellaneous costs were considered in the economic analysis. This included the cost of terminal care.

Estimates of resource use were obtained from literature searches and previous guidelines. The summary table of health care costs is presented below.

Table 42: Healthcare costs

Health states	*Items*	*Value*
A: Pre-progression, PANO/BTZ/DEX	*PANO/BTZ/DEX*[106]	*£5,366 (first treatment phase, cycles 1 to 8)* *£4,562 (second treatment phase, cycles 9 to 16)*
	BTZ/DEX	*£1,837 (first treatment phase, cycles 1 to 8)* *£918 (second treatment phase, cycles 9 to 16)*
	IV administration	*£156*
	Monitoring and tests	*£185.56*
	Adverse events	*PANO/BTZ/DEX: £117.04*
	Total (PANO/BTZ/DEX)	*£6,293 (cycle 1 to 8)* *£5,176 (cycle 9 to 16)*
	Total (BTZ/DEX)	*£2763 (cycle 1 to 8)* *£1,533 (cycle 9 to 16)*
B: Pre-progression, No treatment	*Monitoring costs*	*£185.56 / 2 = £92.78*
C and D: Post-progression, LEN/DEX, POM/DEX or BSC	*LEN/DEX* *Concomitant med.* *POM/DEX* *Concomitant med.* *Other active treatments* *BSC*	*£2,831.69* *£95.20* *£6,098.63* *£67.89* *£1,001* *£2,188*
E: Death	*Terminal care*	*£1,235 lump sum applied on death*

BSC, best supportive care; BTZ, bortezomib; DEX, dexamethasone; IV, intravenous; LEN, lenalidomide; PANO, panobinostat; POM, pomalidomide.

[106] Based on the base case panobinostat price assumption of £776 for the 20mg capsule

Source: Submission Table 58

The following NHS costs were included in the analysis:

- Drug acquisition costs (including IV administration costs for BTZ);
- Treatment monitoring costs;
- Costs for the management of AEs;
- Terminal care costs.

Drug acquisition costs

Apart from the assumed price of PANO, which was set at £476, drug acquisition costs based on the most recent available list price (BNF) were used. Testing costs were drawn from the national schedule of reference costs and other published sources. The costs of managing AEs were based on recent NICE oncology submissions while terminal care costs were obtained from the National Audit Office publication 'End of life care' and attached to each death occurring in the model.

BTZ is dosed per body surface area. The surface area was estimated at 1.81m^2 by utilising average body weight and height of the trial sample. The company present the unit cost of five drugs used in the disease management (**Table 43**).

Table 43: Unit costs and cost per administration for each drug

Drug	*Unit*	*Unit cost*	*Dose*	*Cost/ dose*	*Source*
Panobinostat	*20 mg*	*£776*	*20 mg*	*£776*	*Assumption*
Bortezomib	*3.5 mg*	*£762.38*	*1.3 mg/m^2*	*£512.54*	*BNF*
Dexamethasone	*2 mg*	*£0.78*	*20/40 mg*	*£7.8 / £15.60*	*BNF*
Lenalidomide	*25 mg*	*£208.00*	*25 mg*	*£208.00*	*BNF*
Pomalidomide	*4 mg*	*£423.00*	*4 mg*	*£423.00*	*BNF*

BNF, British National Formulary; for bortezomib vial sharing was assumed in line with UK clinical practice and also to account for the dose intensity as seen in the PANORAMA-1 trial.

Source: Submission Table 53

As PANO/BTZ/DEX and BTZ/DEX regimens are givens as 3-week cycles, Novartis present the cost per 3-week cycle. In response to a clarification question regarding minor differences in cost estimates presented in Tables 55 and 58 of the submission and those presented in the text, Novartis confirmed that the costs per 3-week cycle for PANO/BTZ/DEX and BTZ/DEX should be as reported in the text. Thus, the figures in Table 55 of the submission for these two regimens should be as follows.

Table 44: Cost per 3-week cycle by drug regimen

Regimen	*Cost per 3-week cycle*	*Comments*
PANO/BTZ/DEX	***£5,366*** *(first treatment phase, cycles 1 to 8)* ***£4,562*** *(second treatment phase, cycles 9 to 16)*	*IV administration cost of £156 per treatment to be added for BTZ*
BTZ/DEX	***£1,837*** *(first treatment phase, cycles 1 to 8)* ***£918*** *(second treatment phase, cycles 9 to 16)*	*IV administration cost of £156 per treatment to be added for BTZ*
LEN	*£2,830*	*Applied for 35 3-weekly cycles* *Cost of DEX, £1.94 per cycle and G-*

Regimen	Cost per 3-week cycle	Comments
		CSF, £95 per 3-week cycle to be added
POM	*£6,097*	*Cost of DEX, £1.63 per cycle and concomitant medications, £67.89 per cycle, to be added*
Fourth-line therapy (other active treatments)	*£1,001*	*Gooding et al.*[107]
MRU	*£2,188*	*Gooding et al.*

BTZ, bortezomib; DEX, dexamethasone; G-CSF, granulocyte colony-stimulating factor; IV, intravenous; LEN, lenalidomide; MRU, medical-resource utilisation; PANO, panobinostat; POM, pomalidomide

Source: Adapted from Submission Table 55

The costs for all regimens were converted to costs per 3-week cycle as PANO/BTZ/DEX and BTZ/DEX are administered on the basis of a 3-week cycle. The costs of PANO/BTZ/DEX and BTZ/DEX take account of treatment interruptions and dose reductions permitted in PANORAMA-1. Due to these factors, dose intensities of PANO, BTZ and DEX among PANO/BTZ/DEX patients were estimated to be 80.7%, 75.8% and 87.5%, while those of BTZ and DEX in BTZ/DEX patients were put at 86.7% and 95.1%, respectively. It was assumed that BTZ is administered intravenously in all patients as in the PANORAMA-1 study. The cost of this was set to the adult follow-up outpatient mandatory tariff price for the Haematology speciality from the 2013-14 UK National Tariff. Other drugs are assumed to be administered orally and therefore to involve no administration cost.

In the company's original submission, the dose intensity adjustments were made in both the full trial sample and the subgroup models. However, the response to clarification questions corrected for this in the case of BTZ in the subgroup model as two options were explored, BTZ either being administered 100% intravenously or 100% subcutaneously (See section 6).

In the case of lenalidomide (LEN), the company negotiated a patient access scheme (PAS) under which the costs is met by the company for patients remaining on LEN for more than 26 cycles of four weeks each. Therefore, in the current analysis, LEN costs are applied for 35 3-week cycles. The 3-week cycle cost of pomalidomide (POM) took into account dose interruptions and was informed by the range of (28 day) cycle costs reported in the STA of POM for rrMM.[108] The costs of LLoT, over and above those of POM and DEX were drawn from a study which reported treatments administered and medical resource utilisation (MRU) costs, including clinic attendance, inpatient admissions, supportive therapies, transfusions and blood tests) for double-refractory/intolerant MM patients.

Monitoring costs

In the model, monitoring costs were applied to the pre-progression health states (pre-progression on treatment and pre-progression off treatment) but not the post-progression health states.

These were based variously on NICE TAs, NICE costing templates and the 2013-14 National schedule of reference costs as shown in **Table 47**.

[107] Gooding S, Lau I-J, Sheikh M et al. Double refractory myeloma: analysis of clinical outcomes and medical-resource utilisation in a single centre Blood 2013;122:Abstract 1727.

[108] Celgene. NICE Single Technology Appraisal (STA) - Pomalidomide for relapsed and refractory multiple myeloma. June 2014.

As noted above, the company mentioned bone marrow biopsy and aspirate does in Section 2.4 of the submission however this test is not included in the monitoring costs. The ERG clinical expert confirmed that patients with this condition do not always undergo repeat marrow examinations.

In Table 56 of the submission, the values of frequency of monitoring tests per cycle are in disagreement with the values used in the model. In the table below the ERG has corrected the values using the ones in the model.

Table 45: Monitoring scheme for pre-progression therapy (PANO/BTZ/DEX or BTZ/DEX)

Activity	*Frequency per cycle*
Serum protein assessment	*1.00*
Skeletal survey (bone X-ray)	***0.06***
Lab results – haematology	*1.00*
Lab results – thyroid function test	***0.23***
Lab results – blood chemistry	*1.00*
Specialist visit	***1.00***

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

Source: Submission Table 56

It is stated in the submission "*monitoring costs were assumed to be the same for both PANO/BTZ/DEX and BTZ/DEX and estimated to be £171*". However, in the model, cost of monitoring on treatment is £341.56 and cost of monitoring off treatment is £92.78. Furthermore, Novartis state that "*Based on expert opinion, it was assumed that pre-progression patients who were not on treatment would receive regular monitoring on a 6-weekly basis, hence the average monitoring cost calculated per cycle was half of that applied while on treatment*".

The ERG note that monitoring cost while on treatment should be £186 when excluding IV administration cost of £156 and not £342 as per model. Cost of IV administration of £156 was double counted in the model when calculating the monitoring costs. This error, however, was corrected during the clarification phase for the population of patients who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen (the Appendix 17 of the submission) but not for analysis of patients who have received at least one prior therapy.

The ERG therefore, present the new calculation by applying a correct cost of monitoring while on treatment at £186.

Table 46: Updated incremental cost-effectiveness analysis result with corrected monitoring cost

Technology	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£)*	*Incremental LYG*	*Incremental QALYs*	*ICER (£) versus baseline (QALYs)*	*ICER (£) incremental (QALYs)*
PANO/BTZ/DEX	***£196,570***	*3.570*	*2.404*	***£43,950***	*0.773*	*0.563*	***£ 78,071***	***£78,071***
BTZ/DEX	***£152,619***	*2.797*	*1.841*					

Unit cost per monitoring activity was also presented in the submission and the table is replicated below.

Table 47: Unit costs per monitoring activity

Activity	*Unit cost*	*Source*
Serum protein assessment	*£15*	*NICE TA338, Pomalidomide*
Skeletal survey (bone X-ray)	*£75.00*	*2014, http://www.nice.org.uk/guidance/cg176/resources/cg176-head-injury-costing-template2*
Lab results – Haematology	*£3.00*	*2014, Directly Accessed Pathology Services, Haematology, National schedule of reference costs (2013–2014)*
Lab results – Thyroid function test	*£18.00*	*2014, http://www.nice.org.uk/guidance/ta312/resources/ta312-multiple-sclerosis-relapsingremitting-alemtuzumab-costing-template2*
Lab results – Blood chemistry	*£3.00*	*2014, Directly Accessed Pathology Services, Haematology, National schedule of reference costs (2013–2014)*
Specialist visit	*£156.00*	*2014, Outpatients – Consultant Led, Clinical haematology, National schedule of reference costs (2013–2014)*

NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

Source: Submission Table 57

Miscellaneous cost

The cost of terminal care was also estimated. In order to calculate this, it was assumed that 20% of MM patients will likely need end-of-life care. A one-off terminal cost of £1,235 was applied in the model when a patient dies, adopting the calculations published in TA171. The estimation is reported to be based on the cost of £6,177. No source is indicated in the model or the submission. There is no information on the different elements of costs the estimation of terminal care capture.

5.1.2.6. Discounting

All costs and health benefits were discounted at a 3.5% rate as recommended by NICE.

5.1.2.7. Sensitivity analysis

A range of deterministic sensitivity analysis was provided in the submission. Deterministic one-way sensitivity analysis was performed on sample variables within the model. However no tornado diagram was generated as the output of the one-way sensitivity analysis to illustrate the relative importance of uncertainty across individual parameters in the model.

In addition to deterministic sensitivity analysis, Novartis also presented probabilistic sensitivity analysis (PSA) on parameters which are not subject to sampling variation (e.g. time horizon) except for the price of PANO. Scenario analysis were also carried out by varying input values of parameters.

The critique of sensitivity analysis is discussed further in Section 5.3

5.1.2.8. Model validation

The submission states that the quality control procedures included the verification of the accuracy of model logic and input data by an experienced modeller who had not been involved in the development of the model, with excel formulas checked for consistency with the logic of the model. The statement that '*the model was varied within extreme value beyond what would be considered "reasonable"*' is taken to mean that input parameters were set to extreme values to explore whether the results were

in line with expectations. Model predictions were also compared with observed data where possible. The implication is that the above checks were carried out by Novartis given the further statement in the submission that the model was quality assured by the company which built the model, with an economist not involved in the model's construction reviewing the model for coding errors, inconsistencies and the plausibility of inputs.

As part of the responses to clarification questions, Novartis highlighted errors in the costings used in the subgroup analysis model. The corrected costs and the implications for the cost-effectiveness estimates are presented in this report

5.2. Critique of approach used

The critique of the submission assesses the characteristics of the economic model against the overall specifications of the Reference Case and an established checklist for assessing the quality of economic evaluations. The report then provides a critique of the two main aspects of the cost-effectiveness analysis, namely modelling approach and structure and data inputs, such as clinical effectiveness, AEs, mortality, quality of life and costs.

5.2.1. Critical appraisal frameworks

Novartis' economic analysis was assessed against the requirements of the NICE Reference Case (NICE, 2008[109]) and the BMJ criteria for quality assessing economic evaluations (Drummond et al., 1996[110]).

Table 48: Critical appraisal checklist based on NICE Reference Case (NICE, 2008)

NICE reference case requirement		Critical appraisal	Reviewer comment
Defining the decision problem	The scope developed by NICE	✓	
Comparator	After 1 prior therapy: • BTZ monotherapy • BTZ plus DEX After 2 or more prior therapies: • BTZ plus DEX • LEN plus DEX • Combination chemotherapy regimens with, for example, mephalan and doxorubicin, thalidomide and corticosteroids	?	The choice of BTZ plus DEX as main comparator for 2nd line therapy and LEN plus DEX in 3rd line of therapies was deemed to be appropriate Although BTZ monotherapy is not widely used in clinical practice, it is recommended by TA129 therefore it could have been included.
Perspective on	NHS and PSS	?	The company did not identify any PSS

[109] NICE. Critical appraisal checklist. 2008

[110] Drummond, MF. Jefferson, TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party, British Medical Journal, 313(7052): 275–83. 1996.

NICE reference case requirement		Critical appraisal	Reviewer comment
costs			costs to include in the cost-effectiveness analysis
Perspective on outcomes	All health effects on individuals	✓	
Type of economic evaluation	Cost-effectiveness analysis	✓	
Synthesis of evidence on outcomes	Based on a systematic review	?	Based primarily on the PANORAMA-1 trial
Measure of health benefits	QALYs	✓	
Source of data for measurement of HRQL	Reported directly by patients and/or carers	✓	EORTC QLQ-C30 survey data mapped out onto EQ-5D
Source of preference data for valuation of changes in HRQL	Representative sample of the public	✓	EQ-5D
Discount rate	3.5% per annum for costs and health effects	✓	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✓	

Source: Produced by the ERG

Table 49: Critical appraisal checklist from Drummond and colleagues (Drummond et al. 1997)

Item	Critical appraisal	Reviewer comment
Has the correct patient group/population of interest been clearly stated?	?	There are some confusion in the use of terms rrMM. The trial population is younger than the typically presenting UK population.
Is the correct comparator used?	?	The choice of BTZ plus DEX as main comparator for 2nd line therapy and LEN plus DEX in 3rd line of therapies was deemed to be appropriate. Although BTZ monotherapy is not widely used in clinical practice, it is recommended by TA129 therefore it could have been included.
Is the study type reasonable?	✓	A semi-Markov model structure was used.
Is the perspective of the analysis clearly stated?	✓	UK NHS PSS
Is the perspective employed appropriate?	✓	NHS Reference Costs

Item	Critical appraisal	Reviewer comment
Is the effectiveness of the intervention established?	✓	Estimates of relative effectiveness were derived from a trial (PANORAMA-1). They are likely to be valid. Their generalisability to UK patient may be limited
Has a lifetime horizon been used for analysis, if not has a shorter time horizon been justified?	X	A25-year time horizon was used. After 25 years, virtually 99% of patients modelled are dead.
Are the costs and consequences consistent with the perspective employed?	✓	The company did not identified any PSS costs to include in the cost-effectiveness analysis
Is differential timing considered?	✓	All future costs and benefits are discounted with a 3.5% rate.
Is incremental analysis performed?	✓	
Is sensitivity analysis undertaken and presented clearly?	✓	Deterministic and probabilistic sensitivity analyses are reported.

Source: Produced by the ERG

5.2.2. Critique of the modelling approach and structure

Novartis justify their choice of model structure on the basis that it "corresponds to the expected clinical pathway for management of patients with rrMM" (section 5.2.2 of the submission).

In respect of the choice of health states in the model, the submission states that these are identical with those used in previous NICE STAs. It is noted that the use of two pre-progression health states (on treatment and off treatment) have been used in submissions for LEN for the treatment of MM in those who have received at least one prior therapy and for POM in those with rrMM.

The main reason for employing a Markov model approach is to extrapolate survival beyond the trial period. This is a valid basis for applying fitted curves to the observed data and allows a sufficiently long time horizon to pick up all the important impacts of treatment. It is worth noting that using a time horizon of five years rather than 25 years alters the cost per QALY ratio by less than 10%. The ICER decreases from £79,025 to £72,438.

The ERG acknowledge the appropriateness of finding a best fit model for the survival data observed in PANORAMA-1 in order to extrapolate beyond the time horizon of the trial. However, given that changes in time horizon do not have a marked impact on the cost per QALY ratio, it would have been useful to run a within-trial analysis using survival data drawn exclusively from PANORAMA-1. This is particularly relevant given the way in which the modelled survival functions diverge from the Kaplan-Meier curves in PANO/BTZ/DEX and BTZ/DEX groups. This is discussed further in section5.2.3.3.

The structure of the model in terms of the modelling of patient flows between progression-free and disease progression health states is important insofar as it influences quality of life as well as costs. However, the significance of non-progression appears to be mediated through the TFI, with progression-free survival being associated with discontinuation of treatment when patients have at least a partial response (and remain off treatment until they experience progression).

Given the emphasis on the TFI as the source of quality of life gains, the model could have equally been focussed on this state. In fact, the QALY calculations are not greatly influenced by the progression-free period without treatment (see data presented in Section 5.2.3.4 on quality of life provided by the company to clarification questions from the ERG). This suggests that a simpler, and perhaps more transparent, model structure could have been used which focussed on the TFI explicitly rather than using a two stage approach to modelling PFS.

To the extent that the model uses logistic regression to disentangle the probabilities of progression and of survival, this is an appropriate modelling approach here as its suits problems where the response variable is binary, i.e. progressed or did not progress. Different transformations of the explanatory variables have been carried out to check whether the relationship between explanatory variable(s) and the logarithm of the odds-ratio is linear – an assumption of logistic regression.

The log-logistic model used to model PFS is appropriate for cases in which the probability of disease progression peaks early on before decreasing as individuals stay in the system for longer. This may be relevant in this case if it is likely that once in receipt of treatment a patient's condition can be stabilised quickly.

Novartis report undertaking visual inspections of the fitted curves and using AIC and BIC to assess the best model fit, as well as using clinical plausibility. The AIC and BIC can be used to measure the quality of one model relative to another and should probably not be used for assessing the ultimate feasibility of the model. The distributions chosen to model survival are in principle appropriate and the specification of the resulting fit is detailed in the excel model for the parametric survival model chosen. However, some of the distribution parameters are statistically insignificant, for example those characterising the Gompertz model and the Weibull model for BTZ+DEX. In general, the company did not state the level of significance being used for model selection tests. Furthermore, the distribution parameters for the multi-parameter distributions were not clearly labelled. No details is provided regarding the clinical plausibility or rationale for the choice of parametric survival models.

The method used appears to be consistent with the modelling approach in the documentation. Overall it would greatly benefit the validation of such a model if these steps were broken down rather than being grouped together (i.e. treating death explicitly as a state in its own right). However, a quick confirmation check carried out by Novartis is that the proportions of patients at the end of each cycle who are on study treatment, off study treatment, on LEN+DEX, on LLoT or dead sum to one i.e. everyone who started in either stage A or B is either still in stage A or B, or has moved to C or D or has died.

For patients receiving LEN/DEX, the submission states that patient-level PFS data were assumed to have an exponential distribution to keep the model parsimonious. Contrary to the other clinical input parameters where the testing of several different survival models was used, the risk of progression on LEN/DEX and the risk of post-progression death were assumed to have an exponential distribution to keep the model parsimonious. It is possible that this is due to a lack of statistical evidence to support alternative choices or owing to data availability i.e. small numbers, however no additional justification were provided. An exponential model here would tend to imply that the survival risk is constant through the period, raising the question of whether this is generally consistent with what we would expect in routine clinical practice.

5.2.3. Data inputs

5.2.3.1. Patient group

Given the almost entire reliance on the PANORAMA-1 study for clinical data inputs populating the full trial sample cost-effectiveness model, the objective of the model is to estimate the cost-effectiveness of PANO administered in combination with BTZ and DEX in patients meeting the inclusion criteria of the trial, that is, patients with MM who have received at least one prior therapy. In addition to the overall trial population, three subgroups have been identified for particular attention of the many subgroups of PANORAMA-1 on which subgroup analyses were pre-planned. These are:

- Group 1: Patients who received prior therapy with IMiD plus BTZ;
- Group 2: Patients who received prior IMiD plus BTZ and ≥2 prior lines of treatment;
- Group 3: Patients with 2 to 3 prior lines of treatment.

However, as explained in Section 4.2.7, no information is presented on Group 3.

In section 4.10 of the submission, it is noted that "*for the economic analysis, data for the relative efficacy of PANO/BTZ/DEX vs. LEN/DEX is required as LEN/DEX is a relevant comparator for panobinostat triplet therapy in the management of rrMM in the third-line setting or later*".

One approach to incorporating this potentially relevant comparator into the analysis would have been to estimate the costs and QALYs of PANO/BTZ/DEX relative to both comparators, that is, BTZ/DEX (using matching data from the PANO/BTZ/DEX arm in PANORAMA-1) and LEN/DEX (using MM-009 and MM-010 data) for the relevant subgroups of the PANORAMA-1 trial. The approach adopted by Novartis was to carry out a separate cost-effectiveness analysis of PANO/BTZ/DEX vs. LEN/DEX for the population of patients who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen (in the Appendix 17 of the submission). Thus, the option of BTZ/DEX was not evaluated alongside PANO/BTZ/DEX and LEN/DEX as a possible therapy in patients who have received two or more prior lines of therapy including an IMiD and BTZ (Group 2). This is despite this group being represented in the PANORAMA-1 study. As a result, it is not possible to compare the cost-effectiveness of PANO/BTZ/DEX and BTZ/DEX in this subgroup and this raises questions about the most appropriate comparator in these patients.

A possible argument against using BTZ/DEX as a comparator in the cost-effectiveness analysis is that it is not consistent with UK clinical practice. Such a justification is not used in the submission and, moreover, is problematic given that the cost-effectiveness analysis comparing PANO/BTZ/DEX with BTZ/DEX is based on the full data set from PANORAMA-1. From a cost-effectiveness perspective, if a subgroup of these patients is being treated in the trial in a way which does not conform to UK clinical practice, this raises the question of whether or not these patients should have been excluded from the primary cost-effectiveness analysis. The ERG conclude that it would have been possible, and relevant, to incorporate BTZ/DEX as a comparator in the cost-effectiveness analysis applicable to the subpopulation who have received two or three prior lines of therapy including an IMiD and BTZ and presented in the Appendix 17 of the submission.

Although age is mentioned as one of the groups for which subgroup analysis was pre-planned, it would have been relevant to estimate the cost-effectiveness of PANO/BTZ/DEX vs. BTZ/DEX for different starting ages in the model given that, in the UK, nearly 60% of patients are estimated to be diagnosed at the age of 70 or older and the median age at diagnosis is 73.1 years. This compares with a starting age in the model of 62.1 years.

5.2.3.2. Clinical effectiveness data

Most of the effectiveness data for the full trial sample analysis in the economic model was drawn from PANORAMA-1. The one exception is that progression data for those receiving LEN/DEX after failure to the initial treatment came from MM-009 and MM-010 as data for progression in patients receiving subsequent antineoplastic treatment after PANO/BTZ/DEX or BTZ/DEX was not collected in the PANORAMA-1 trial.

The health states between which patients move in the model were defined in terms of progression or non-progression of illness. The risk of progression or death in a given cycle was modelled by fitting survival functions to Kaplan-Meier plots of patient level PFS data. Because the risk of progression and the risk of death were both required by the model, the proportion of patients who progressed relative to those who had a PFS event (death or disease progression) was estimated for each cycle by a logistic regression. The model appears to follow the structure set out in the , as we have described in section 5.1.2.2, although a more intuitive explanation of how the health states presented in Figure 37 in the submission correspond to the labels used in the excel model.

A similar survival analysis approach was adopted to the risk of treatment discontinuation. The modelled survival functions appeared to be implemented appropriately and transition probabilities similarly derived from the survival functions using standard methods.[111]

The fitting of survival functions to the observed data has not been replicated as part of this critique as the ERG have not had access to patient-level data from PANORAMA-1, MM-009 or MM-010. Neither have the ERG replicated the results of the indirect treatment comparisons analysis. However, the following section makes some observations on the differences between the modelled survival estimates used in the cost-effectiveness calculations and the survival observed in PANORAMA-1.

In section 7, we explored the impact on the ICER if patients were not required to discontinue BTZ therapy despite having less than minimal response at cycle 4, as per PANORAMA-1 trial, in order to reflect the efficacy used in the control arm of the model.

5.2.3.3. Mortality data

Modelled survival in the cost-effectiveness analysis should mimic the observed survival in PANORAMA-1 as all the mortality data in the full trial sample model, including for patients who proceed to LEN/DEX after PANO/BTZ/DEX or BTZ/DEX (although data on progression in this group was not collected as part of PANORAMA-1 and is based on MM-009 and MM-010 studies), is drawn from the trial.

The ERG noted that the modelled mean survival in the PANO group was greater than the median survival reported by PANORAMA-1 at the 18th August 2014 interim analysis (mean of 42.84 vs. median of 38.24 months) but that the reverse was true fort the PBO group (mean of 33.56 vs. a median of 35.38 months).

Two issues were raised by Novartis by way of clarification:

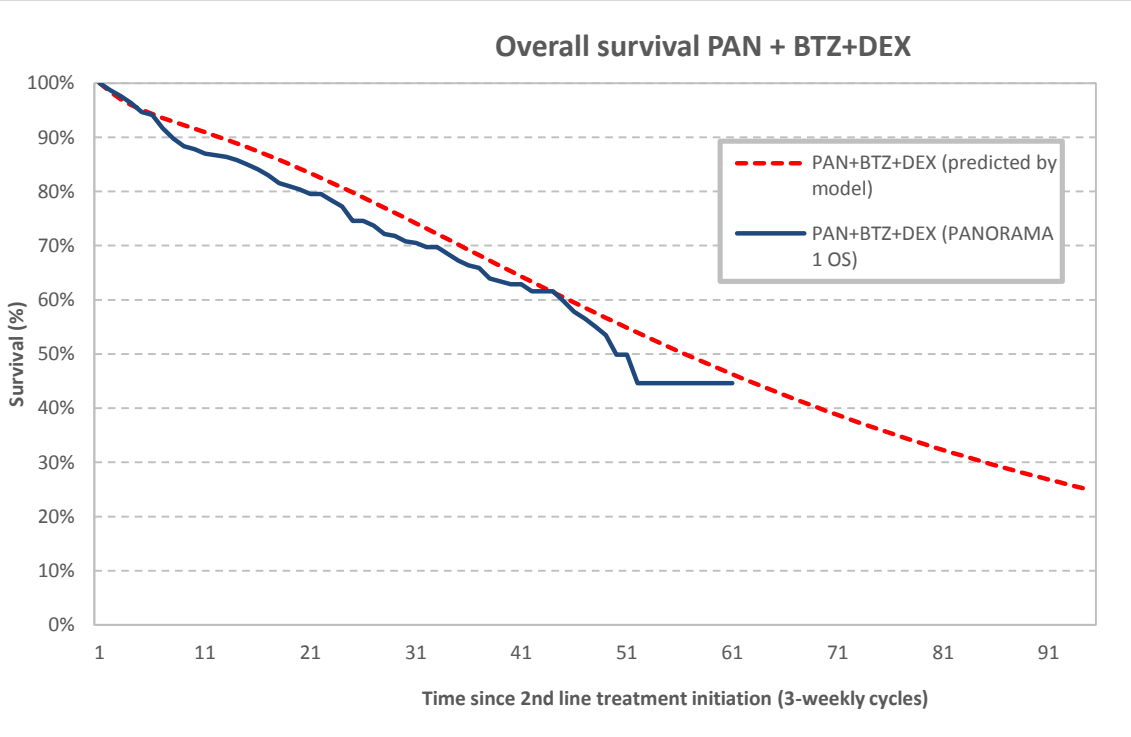
[111] Latimer, N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011.

- *"In line with the modelled English clinical practice, post-progression survival in the model is based on a subset of the PANORAMA-1 population who received LEN/DEX as subsequent treatment";*
- *"In line with the modelled English clinical practice related to NICE TA 129 and the BTZ label, stopping rules were applied (at cycle 4 and cycle 8, per label) on the BTZ arm of the model which changes the course of the treatment when compared to the PANORAMA-1 trial".*

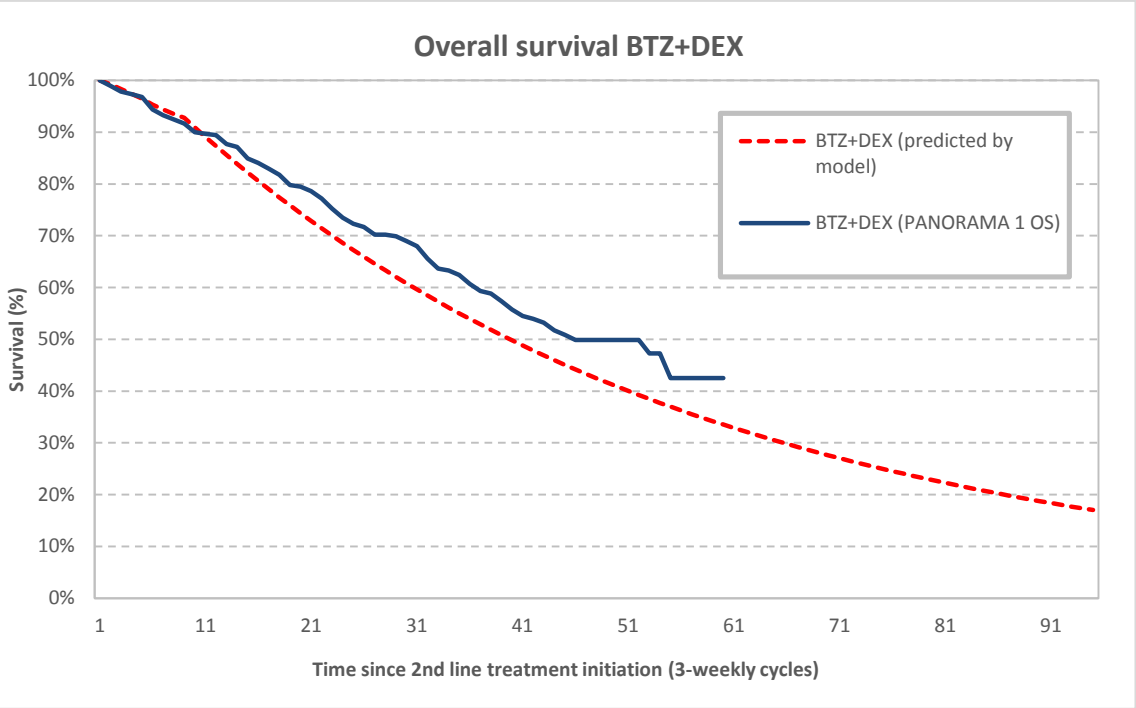
The first point should not unduly affect the comparison of the PANO/BTZ/DEX and BTZ/DEX groups in the model as opposed to the PANORAMA-1 study since, presumably, those receiving LEN/DEX in the trial are also those who are in post-progression survival. Moreover, both groups will include patients receiving LEN/DEX, limiting the impact on the comparison between groups of this (potential) departure from the trial results.

The second point may have some relevance as it applies to the BTZ/DEX arm only, although it seems implausible that the stopping rules introduced into clinical practice would disadvantage BTZ/DEX patients in terms of survival. If this was the case, it would make sense to undertake a scenario analysis in which the trial findings for survival were substituted for the modelled results. This would be particularly useful in light of the observation that the model tends to overestimate survival in the PANO/BTZ/DEX group and underestimate survival in the BTZ/DEX group when compared with the Kaplan-Meier curves. The comparison between the Kaplan Meier plots and curves as predicted by the model for OS for the two treatment arms is reproduced in Figure 26 below.

Figure 26: Kaplan–Meier curve and OS curve of the model



Source: Adapted from the model



Source: Adapted from the model

5.2.3.4. Health related quality of life

Quality of life data was also collected within the trial although it was not designed for the purposes of generating cost per QALY estimates as it did not collect patient data on a utility measure (such as EQ-5D). The submission identified, from the literature, a study which mapped from the two EORTC measures used in PANORAMA-1 on to EQ-5D in a patient population similar to that enrolled in the trial.

The submission states that "*cycle-specific mapped utility values were lower for PANO/BTZ/DEX than for BTZ/DEX at all time points*". Mean utility values for the full PANORAMA-1 population are given as 0.706 in the PANO/BTZ/DEX group and 0.725 in the BTZ/DEX group. It is reported that the overall mean values were used for the pre-progression on treatment states.

In response to a clarification question regarding mean survival data used in the cost-effectiveness analysis, Novartis provided the amount of time spent in the four states for which utilities have been separately estimated. These are consistent with the ones used in the model. Using these values along with the utilities reported in **Table 39**, gives an overall mean QoL (calculated from the utilities of each health state weighted by time in the state) of 0.67 for PANO/BTZ/DEX and 0.66 calculated for the BTZ/DEX. This average is consistent with the QALYs on which the cost-effectiveness calculations are based, as calculated in **Table 50** below. However, this is surprising in light of the difference in safety profile of the two treatments.

Table 50: Utility scores, life years and calculated QALYs

	PANO/BTZ/DEX	BTZ/DEX	PANO/BTZ/DEX	BTZ/DEX	PANO/BTZ/DEX	BTZ/DEX
	Life years		Utilities		QALYs – calculated	
Pre-progression Tx	0.50	0.30	0.706	0.725	0.353	0.218
Off treatment	0.70	0.20	0.762	0.762	0.533	0.152

	PANO/BTZ/ DEX	BTZ/DEX	PANO/BTZ/ DEX	BTZ/DEX	PANO/BTZ/ DEX	BTZ/DEX
LEN+DEX	1.15	1.15	0.64	0.64	0.736	0.736
POM+DEX/BSC	1.22	1.14	0.64	0.64	0.781	0.730
Total	**3.57**	**2.80**			**2.403**	**1.836**
Average QoL					0.67	0.66

Source: Produced by the ERG

If the utility scores in the two groups are intended to capture the relatively less favourable incidence of AEs in PANO/BTZ/DEX compared with BTZ/DEXD patients with a higher proportion of PANO than PBO patients discontinuing owing to AEs (as explained in section 4.5 of the submission), then the discussion of safety profiles in the context of utilities suggests that the utilities underpinning the benefits of PANO reported in the Novartis analysis may overstate the actual benefits of PANO in combination with BTZ/DEX. This is before taking account of any decrement associated with the AEs, which were not reported in PANORAMA-1 but which might have been identified by a literature search for AEs.

5.2.3.5. Resources and costs

The ERG are generally satisfied with the sources used to obtain unit costs for the economic model. Estimates of resource use were obtained from literature searches and previous guidelines.

Novartis present the cost of AEs and use unit costs per monitoring activity in the economic model. The ERG could not find the cited cost of serum protein assessment of £15 in the NICE guideline TA338 on POM[112]. In addition, skeletal bone survey costed at £75 cannot be verified either as it could not be found in the costing template of head injury[113]. The rest of the monitoring costs have been verified by the ERG.

AEs costs were also confirmed by the ERG. Novartis present a cost of anaemia of £1,155. The ERG found that the referenced £1,155 figure is for Iron Deficiency Anaemia with CC (Complication and Comorbidity) Score 0-1 and is the lowest unit price among other Iron Deficiency Anaemia conditions varying by CC Score. It is not clear to the ERG why this particular cost was used in the model.

Novartis present a cost of £355 for hypokalaemia taken from NHS 2014 reference costs, however, the ERG searched the code and description of the procedure indicated by the company but the costs associated with this AE do not match Novartis costs. We found a cost estimate of £304 for admitted patient care, a cost estimate of £462 for outpatients and other (not specified) cost of £596. Therefore the ERG are not clear where the cost was taken from and if it includes hospital stay or not. This implies that the cost of hyponatraemia is also probably a mistake as it is assumed to be the same as hypokalaemia.

Novartis present a cost of £167 for neutropenia also taken from NHS 2014 reference costs, however, the ERG searched the code and description of the procedure as well but the costs associated with this

[112] National Institute for Health and Care Excellence. Technology Appraisal 338. Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib. 2015. Available from : https://www.nice.org.uk/guidance/ta338

[113] NICE. Head injury : triage, assessment, investigation and early management of head injury in children, young people and adults.2014. Available from : http://www.nice.org.uk/guidance/cg176/resources/cg176-head-injury-costing-template2

do not match the cost presented. We found a cost estimate of £155 for admitted patient care, a cost of £179 for outpatient and a cost of other (not specified) at £164. This implies that the cost of Lymphopenia is probably also wrong as it is assumed to be the same as neutropenia. However, the ERG expert noted that the cost of Lymphopenia should not be included in the calculations.

Novartis present the cost of lobar, atypical and viral pneumonia. The cited cost is for lobar, atypical and viral pneumonia with CC scores 0-2 that is the lowest unit cost for such event. The unit cost for lobar, atypical and viral pneumonia depending on the CC score varies from £1,433 to £5,413. Again, the ERG is not clear why Novartis took the lowest price.

The cost for thrombocytopenia (SA12K) of £604 was not found. The ERG checked the code SA12K and it corresponds to thrombocytopenia with CC score 0-1 with a cost of £530. The cost figures of thrombocytopenia with other CC scores are also available. However, it is indicated in the model that the cost for thrombocytopenia is from 2013. The ERG is not clear whether this is a typo or not and if not why the costs was not taken from the 2014 reference costs.

Additionally, the ERG clinical expert commented on the frequency of thyroid function laboratory tests and stated that the test is typically administered no more than every 6 months. However, the Table 56 of the full trial sample analysis states that thyroid function test is administered per cycle. Furthermore, the specialist visits should be conducted every 2 to 3 cycles. However, as noted above, specialist visits are applied considered one per cycle. The frequency of activities for the disease monitoring was mismatched with the model inputs. These have been corrected in Section 7**Error! Reference source not found.**.

Although costs were inflated to 2014 in the model, the company fail to note this in the submission that a number of costs were inflated to 2014.

5.2.3.6. AEs

The estimation of the AE occurrence is not well explained in the submission. The figures reported as the number of AEs observed in the safety set of the full PANORAMA-1 trial population (**Table 40**) do not match the ones reported in the safety profile of the PANORAMA-1 trial (Table 17). We have compared the incidence from the submission in the **Table 51** below when possible. Asthenia and fatigue are reported together and some of the AEs are not reported in table in Table 17. Therefore we cannot compare these AEs.

Table 51: Number of AEs in the full PANORAMA-1 trial population (safety set)

	PANO/BTZ/DEX (n = 381)		BTZ/DEX (n = 377)	
Grade ¾ AEs	N (Table 17 of this report)	N (Table 40 of this report) with corrected figures	N (Table 17 of this report)	N (Table 40 of this report) with corrected figures
Anaemia	69	63	72	60
Asthenia	N/A	36	N/A	14
Diarrhoea	95	97	30	30
Fatigue	N/A	65	N/A	33
Hypokalaemia	N/A	73	N/A	24
Hyponatraemia	N/A	37	N/A	13
Lymphopenia	N/A	**47**	N/A	**28**
Neutropenia	130	92	42	30
Pneumonia	50	48	38	39
Thrombocytopenia	255	217	118	94

Source: Submission Table 59 corrected by the ERG using the submission Table 34

Expert opinion sought by the ERG confirmed that the safety profile of PANO was a realistic description of the range of side effects seen and corresponds to what is described in the literature both for this drug and other deactylase inhibitors. However, our expert also pointed out that the cost of AE for Lymphopenia should be zero as it has no direct clinical relevance since infections are being treated as and when they arise.

It is not clear to the ERG why the decrement in utilities associated with the AEs were not taken into account and included in the model. Additionally, Novartis did not provide a justification for the non-inclusion of adjustment to utilities to reflect the AEs. As mentioned above in section 5.2.3.4 , even if not collected during the trial a systematic literature search would have helped to identify appropriate utility decrements. Contrary to what is suggested in the DSU technical support document 12, [114] there is lack of rigorous method to ensure that AEs were captured within the utilities used. This is a concern to the ERG, particularly in light with the differences in safety profile between the two treatments compared.

5.2.4. Sensitivity analysis

A range of sensitivity analyses was provided in Novartis's submission:

- Probabilistic sensitivity analysis (PSA);
- Deterministic sensitivity analysis; and
- Scenario analysis.

These are reviewed in depth in the section below.

5.3. Results included in company's submission

This section presents a summary of the results of Novartis' model for the full trail sample.

5.3.1. Deterministic results

[114] Ara, R., Wailoo, A.J. NICE DSU Technical Support Document 12: The use of health state utility values in decision models. 2011. Available from: http://www.nicedsu.org.uk

5.3.1.1. Base case

Base case inputs of the model are presented in Table 61 of the submission alongside Table 62 which summarises the assumptions used by the company. The ERG present Novartis's base case results in Table 52. The base case analysis is based on a cost of 20mg capsule of PANO set at £776 since there is no approved price for PANO. The company say that the final price will be determined upon granting of EMA marketing authorisation.

Table 52: Base-case incremental cost effectiveness analysis results

Technologies	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£)*	*Incremental LYG*	*Incremental QALYs*	*ICER (£) versus baseline (QALYs)*	*ICER (£) incremental (QALYs)*
PANO/BTZ/DEX	*£197,922*	*3.570*	*2.404*	*£44,487*	*0.773*	*0.563*	*£79,025*	*£79,025*
BTZ/DEX	*£153,434*	*2.797*	*1.841*					

BTZ, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PANO, panobinostat; QALYs, quality-adjusted life years

Source: Submission Table 63

However, as noted before, there was an error in the model whereby the cost of IV administration was double counted. The ERG replicate the cost-effectiveness analysis results here with the correct monitoring cost. This table does not include any other corrections.

Table 53: Updated incremental cost-effectiveness analysis result with corrected monitoring cost

Technologies	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£)*	*Incremental LYG*	*Incremental QALYs*	*ICER (£) versus baseline (QALYs)*	*ICER (£) incremental (QALYs)*
PANO/BTZ/DEX	**£196,570**	3.570	2.404	**£43,950**	0.773	0.563	**£78,071**	**£78,071**
BTZ/DEX	**£152,619**	2.797	1.841					

Source: Submission Table 63 corrected by the ERG

Novartis present median PFS and OS estimates of the model results in comparison with clinical data as presented in the table below. Importantly, no mature OS data for the PANORAMA-1 trial have been reported in this submission.

Table 54: summary of model results compared with clinical data

Outcome	*Clinical trial result*	*Model result*
Median PFS (PANO/BTZ/DEX)	*12.0 months*	*12.0 months*
Median OS (PANO/BTZ/DEX)	*33.6 months*	*38.3 months*
Proportion of patients experiencing adverse events (PANO/BTZ/DEX)	*Rates obtained from trial*	*Rates obtained from trial*

BTZ, bortezomib; DEX, dexamethasone;OS, overall survival; PANO, panobinostat; PFS, progression-free survival.

Source: Submission Table 64

In the clarification stage the company said that patient level data were used in the model, hence means was not used as input data for PFS and OS. The ERG noted that the modelled mean survival in the PANO group was greater than the median survival reported by the PANORAMA-1 trial at the 18th

August 2014 interim analysis (mean of 42.84 vs. median of 38.24 months) but it was the reverse for the PBO group. This was discussed in Section 5.2.3.3.

Novartis also present a summary of QALYs gained by health state. The company explain that higher QALY gain in patients receiving PANO/BTZ/DEX compared to BTZ/DEX is mainly due to the longer PFS in the for PANO arm resulting in longer treatment-free period. It was calculated that the patients who receive PANO/BTZ/DEX regimen expect to achieve 2.40 QALYs (discounted) whereas patients receiving BTZ/DEX regimen will achieve 1.84 QALYs (discounted). Therefore the estimated incremental gain is 0.563 QALYs. The summary of QALY gain of PAN/BTZ/DEX over BTZ/DEX broken down by health state is presented in Table 65 of the submission.

Table 55: Summary of QALY gain by health state

Health state	*QALY intervention (PAN/BTZ/DEX)*	*QALY comparator (BTZ/DEX)*	*Increment*	*Absolute increment*	*% absolute increment*
Pre-progression, treatment	*0.353*	*0.218*	*0.135*	*0.135*	*24%*
Pre-progression, No treatment	*0.536*	*0.155*	*0.381*	*0.381*	*68%*
Post-progression, LEN/DEX	*0.734*	*0.734*	*0.000*	*0.000*	*0%*
Post-progression, LLoT	*0.780*	*0.732*	*0.048*	*0.048*	*8%*
Total	***2.404***	***1.841***	***0.563***	***0.564***	***100%***
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

BTZ, bortezomib; DEX, dexamethasone, LEN, lenalidomide, LLoT, last line of treatment; PANO, panobinostat; QALY, quality-adjusted life year.

Source: Submission Table 65

Based on a cost of PANO at £776, Novartis present the summary of cost by health state in Table 66 of the submission. This table is replicated in **Table 56** below. Please note that some of the costs should be amended due to updated cost of the disease management and Lymphopenia. A summary of the predicted resource use by category of cost, such as drug cost, AE, etc. are also presented in Table 67 of the submission.

Table 56: Summary of costs by health state

Health state	*Cost intervention (PAN/BTZ/DEX)*	*Cost comparator (BTZ/DEX)*	*Increment*	*Absolute increment*	*% absolute increment*
Pre-progression, treatment	*£52,552*	*£14,708*	*£37,843*	*£37,843*	*85%*
Pre-progression, No treatment	*£1,132*	*£328*	*£804*	*£804*	*2%*
Post-progression, LEN/DEX	*£46,256*	*£46,303*	*-£47*	*£47*	*0%*
Post-progression,	*£96,898*	*£90,978*	*£5,920*	*£5,920*	*13%*

Health state	*Cost intervention (PAN/BTZ/DEX)*	*Cost comparator (BTZ/DEX)*	*Increment*	*Absolute increment*	*% absolute increment*
LLoT					
Death	*£1,084*	*£1,117*	*-£33*	*£33*	*0%*
Total	*£197,922*	*£153,434*	*£44,487*	*£44,648*	*100%*
from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

BTZ, bortezomib; DEX, dexamethasone, LEN, lenalidomide, LLoT, last line of treatment; PANO, panobinostat; QALY, quality-adjusted life year

Source: Submission Table 66

5.3.1.2. Deterministic sensitivity analysis

The submission allows for uncertainty around parameter inputs in three ways:

- Deterministic one-way sensitivity analysis on uncertain parameters within the model except on the acquisition cost of PANO;
- Scenario analysis varying input values of parameters which are not subject to sampling variation (e.g. time horizon), but excluding the price of PANO.

In the deterministic sensitivity analysis, ranges of cost per QALY results were obtained by varying input parameters one at a time between the upper and lower bounds of the 95% confidence interval. If the confidence interval was not reported, upper and lower limits for the sensitivity analysis were generated by adding or subtracting two times 20% of the mean.

The upper and lower confidence limits of PFS gave cost per QALY estimates ranging from £29,015 (a 63% reduction compared with the base case) to £228,683 (a 189% increase on the base case).

The deterministic sensitivity analysis results were presented by Novartis in Table 69. The company say that in general model outcomes (i.e. QALYs, costs and ICERs) were most sensitive to the regression parameters associated with progression i.e. PFS, proportion of "*progressors*" (which is assumed to be the proportion on patients progressing on LEN/DEX). The main driver to incremental QALYs was the utility values applied for TFI, whereas the progression-related parameters and treatment discontinuation rates appear to impact the incremental costs significantly. In general, cost-related parameters did not influence the model results.

Importantly, the names of input variables presented in Table 61 of the submission do not correspond to the deterministic results outputs presented in Table 69. For instance, it is not clear which PFS parameters have the most influence. Additionally, the one-way sensitivity analysis is not present in the excel model and no tornado diagram was not generated. This make it very difficult for the ERG to judge the relative importance of uncertainty across uncertain parameters in the model and commend on the company's conclusions.

5.3.1.3. Scenario analysis

Here, the ERG list the assumptions of scenario analysis that were made by Novartis in the cost-effectiveness model:

- Dose reductions observed in the PANORAMA-1 trial were ignored;
- A discount rate of 5%, rather than 3.5%, was used;
- Time horizons of 5 and 10 years were used instead of 25 years;

- PFS was modelled with parametric functions other than the Weibull model;
- The proportion of "*progressors*" in PFS for PANO/BTZ/DEX, BTZ/DEX responders, which is assumed to be the proportion of patients progressing was modelled using raw trial data rather than logistic regression;
- Time to discontinuation was based on Kaplan-Meier estimates rather than a loglogistic model.

Modelling PFS with other parametric functions than the Weibull function (as done in the base case model) provides lower ICERs in all cases, however the biggest impact on the ICER was observed when modelling PFS with a loglogistic or lognormal function, resulting in decreasing the ICER by 33% and 31%, respectively. The ICER remained above £50,000 per QALY in all scenarios. The scenario analysis results were presented in Table 71 of the submission.

It is worth noting that BTZ modelled outcomes were not compared, for internal validation, against the corresponding observed outcomes in the clinical trial data source for the model. The company claim that this was this was is because the model includes assumptions on the treatment pathway to replicate the UK clinical practice and BTZ label (i.e. stopping rules at cycle 4 and cycle 8). The ERG have explored the impact on the ICER of not implementing a stopping at cycle 4 in section **Error! Reference source not found.**.

5.3.2. Probabilistic sensitivity analysis results

For the input parameters assigned to a probability distribution in the PSA, the following distributions were applied:

Table 57: Input parameters and distributions in the PSA

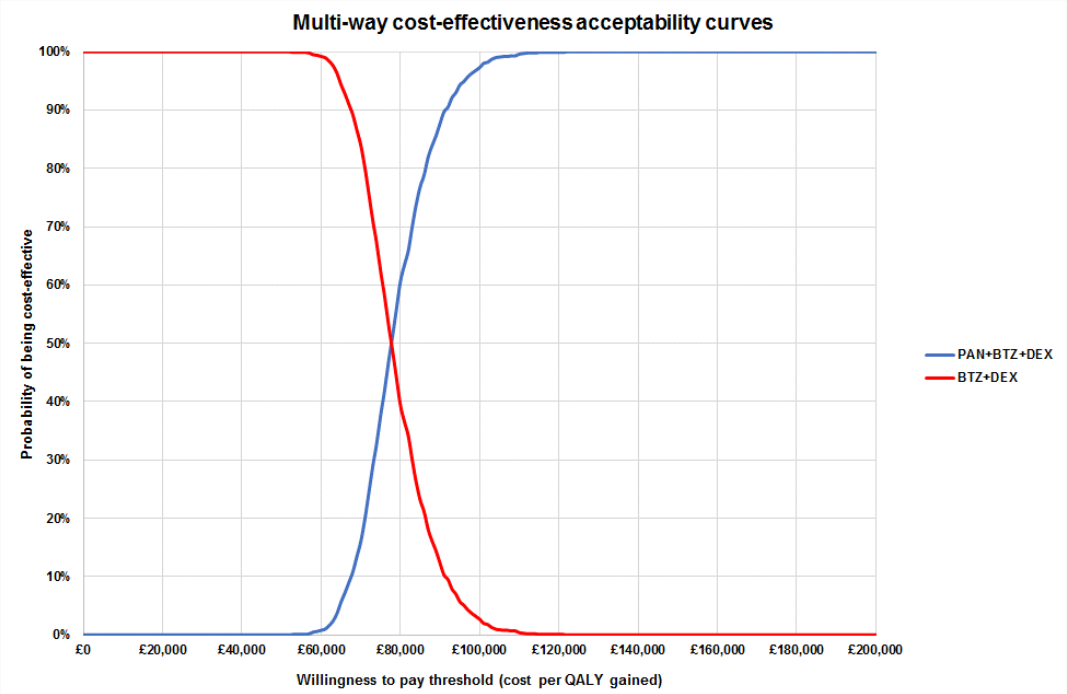
Variable	Normal	Multivariate normal	Beta	Gamma
Risk of progression or death		✓		
Risk of progression (and risk of death)		✓		
Risk of treatment discontinuation (PANO/ BTZ/ DEX and BTZ/DEX cycles 1 to 4)		✓		
Risk of treatment discontinuation (BTZ/DEX responders)	✓			
Risk of progression (BTZ/DEX cycles 1 to 4 without disease progression and on LEN/DEX)	✓			
Risk of death	✓			
Response			✓	
AEs			✓	
Utilities			✓	
Unit costs				✓

Source: Produced by the ERG

Correlation between parameters was taken into account if parameters were simulated from a multivariate normal distribution. Under the base case price for PANO, PSA indicated that the probability of PANO/BTX/DEX being cost effective was 50% at a willingness to pay (WTP) threshold of £ £78,000 per QALY gained. At WTP thresholds of £20,000, £30,000, £50,000 and £100,000, the probabilities of PANO/BTZ/DEX being cost-effective were 0%, 0%, 0% and 97%, respectively. This is shown in the multi-way cost-effectiveness acceptability curve presented in **Figure 27** below. The CI around key model outcomes are presented in the table below. Please note that these numbers are

likely to change when the correct monitoring cost is applied and the cost for Lymphopenia is set at zero. This is investigated in section **Error! Reference source not found.**.

Figure 27: Multi-way cost-effectiveness acceptability curves for PANO/BTZ/DEX and BTZ/DEX, discounted analysis



BTZ, bortezomib; DEX, dexamethasone; PAN(O), panobinostat; QALYs, quality-adjusted life years

Source: Submission Figure 49

The PSA resulted in the following 95% Cis around key model outcomes presented in **Error! Reference source not found.** below:

Table 58: CI around key model outcomes

	Cost	*Incremental cost*	*QALYs*	*Incremental QALY*	*ICER (QALY)*
PANO/BTZ/DEX	*£199,405 (£140,614 to £271,621)*	*£44,144 (£33,962 to £56,360)*	*2.40 (1.97 to 3.01)*	*0.56 (0.39 to 0.72)*	*£79,025*
BTZ/DEX	*£155,261 (£100,547 to £225,395)*		*1.86 (1.47 to 2.38)*		

BTZ, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; PANO, panobinostat; QALYs, quality-adjusted life years

Source: Submission Table 68

In the submission, Novartis present the scatter plot of simulated total QALYs in comparison with the cost of both treatment arms (Figure 47 and 48 in the submission) as well as a cost-effectiveness acceptability frontier.

6. Economic evaluation: subgroup analysis – people who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen

In this chapter, we assess the economic analysis submitted by Novartis in the Appendix 17 of the submission, which considered the subgroup of patients who had at least two prior lines of treatment including an IMiD and a BTZ based regimen. The CHMP adopted a positive opinion recommending the granting of a marketing authorisation or PANO in combination with BTZ and DEX for treatment of relapsed and/or refractory multiple myeloma for this subgroup, i.e. patients who have received at least two prior regimens including an IMiD and a BTZ [115].

6.1. Overview of company's economic evaluation

6.1.1. Summary of Novartis' systematic review of cost-effectiveness studies

6.1.1.1. Description of company's search strategy and comment on whether the search strategy was appropriate

For the critique of search strategy to identify published cost-effectiveness studies refer to Section 5.1.1.1

6.1.1.2. Search results

The search result of cost-effectiveness studies are discussed Section 5.1.1.2.

6.1.1.3. Additional search

To identify and evaluate previously published pharmacoeconomic models and HTAs in rrMM setting Novartis conducted a targeted review, searching in PubMed and on the National Institute for Health and Care Excellence (NICE) website. The ERG believe the targeted review to be appropriate for this exercise. The company aimed to extract relevant models published in the last 5 years. No explanation on why this timeframe was chosen. However, in section 1.1.2 Novartis state that "*the economic evaluations were fairly recent; the earliest was published in 2007 whereas the latest was published in 2014*." One of the studies is dated October 2007[116]. This however, contradicts an earlier claim where the company state the targeted search was conducted to identify models published in the last 5 years. Also another study, Green et al. is dated June 2009[117]. Therefore, the ERG are not clear about which parameter limits were applied to this search.

[115] EMA. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003725/smops/Positive/human_smop_000846.jsp&mid=WC0b01ac058001d127 (Accessed 30/06/15)

[116] National Institute for Health and Care Excellence. Technology Appraisal 129: Bortezomib monotherapy for relapsed multiple myeloma. October 2007. Available at: www.nice.org.uk/TA129. (Accessed 4 October 2013).

[117] Green C, Bryant J, Takeda A et al. Bortezomib for the treatment of multiple myeloma patients. Health Technol Assess 2009;13 (Suppl 1):29–33.

Novartis reviewed 8 economic evaluations dated between 2007 and 2014. The extracted findings would inform the modifications of the previously conducted analysis (we assumed that the company refer to the analysis of the patient population represented by the full PANORAMA-1 trial sample). The summary of published models is presented in the table below. As noted above, quality assessment was performed for only three of them (Section 5.1.1). The company do not make a conclusion statement from their review. After presenting a table of summary of published pharmacoeconomic models (also presented below), Novartis then discuss de novo analysis.

Table 59: Summary of published pharmacoeconomic models

Author	Treatments compared	Model type	Health states	Time horizon (Years)	Adverse events included	Country
Hornberger et al, 2010[118]	*BTZ DEX LEN/DEX*	*Partitioned survival model*	*Pre-progression Post-progression Death*	*10*	*Yes*	*Sweden*
Brown et al, 2013[119]	*DEX LEN/DEX*	*Individual simulation model*	*Pre-progression Post-progression Death*	*30*	*Yes*	*England and Wales*
Fragoulakis et al 2013[120]	*LEN/DEX BTZ*	*Discrete event simulation model*	*Pre-progression Post-progression Death*	*Individual level lifetime*	*Yes*	*Greece*
Möller et al, 2011[121]	*LEN/DEX BTZ*	*Discrete event simulation model*	*Pre-progression Post-progression Death*	*Individual level lifetime*	*Yes*	*Norway*
Green et al, 2009[122]	*BTZ HiDEX*	*Semi-Markov state-transition model*	*On treatment regimen i Death whilst on treatment regimen i*	*15 years*	*No*	*England, Wales*
NICE HTA 2007[123]	*BTZ HiDEX*	*Semi-Markov state-transition model*	*NA*	*NA*	*Yes*	*England, Wales*
NICE HTA 2009, 2013[124]	*LEN/DEX BTZ BEN and other chemotherapy agents*	*Partitioned survival model*	*Pre-progression on Tx Pre-progression off treatment Post-progression*	*25 years*	*Yes*	*England, Wales*
NICE HTA	*POM*	*Partitioned survival*	*Pre-progression on*	*25 years*	*Yes*	*England,*

[118] Hornberger J, Rickert J, Dhawan R et al. The cost-effectiveness of bortezomib in relapsed/refractory multiple myeloma: Swedish perspective. Eur J Haematol 2010;85 484–91.

[119] Brown RE, Stern S, Dhanasiri S, Schey S. Lenalidomide for multiple myeloma: cost-effectiveness in patients with one prior therapy in England and Wales. Eur J Health Econ 2013;14 507–14.

[120] Fragoulakis V, Kastritis E, Psaltopoulou T, Maniadakis N. Economic evaluation of therapies for patients suffering from relapsed-refractory multiple myeloma in Greece. Cancer Manag Res 2013;5 37–48.

[121] Moller J, Nicklasson L, Murthy A. Cost-effectiveness of novel relapsed-refractory multiple myeloma therapies in Norway: lenalidomide plus dexamethasone vs bortezomib. J Med Econ 2011;14 690–7.

[122] Green C, Bryant J, Takeda A et al. Bortezomib for the treatment of multiple myeloma patients. Health Technol Assess 2009;13 (Suppl 1):29–33.

[123] National Institute for Health and Care Excellence. Technology Appraisal 129: Bortezomib monotherapy for relapsed multiple myeloma. October 2007. Available at: www.nice.org.uk/TA129. (Accessed 4 October 2013).

[124] National Institute for Health and Care Excellence. Technology Appraisal 171: Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. June 2009. Available fromt: http://www.nice.org.uk/TA171. (Accessed 4 October 2013).

Author	Treatments compared	Model type	Health states	Time horizon (Years)	Adverse events included	Country
2014[125]	*BTZ/DEX* *THAL/DEX/CYC* *BEN/THAL/DEX*	*model*	*Tx* *Pre-progression off treatment* *Post-progression*			*Wales*

BEN, bendamustine; BTZ, bortezomib, CYC, cyclophosphamide; DEX, dexamethasone; HiDEX, high dose dexamethasone; HTA, Health technology Assessment; LEN, lenalidomide; NA, not applicable; NICE, National Institute for Health and Care Excellence; POM, pomalidomide; THAL, thalidomide; Tx, treatment.

Source: Novartis submission, Appendix 17 Table 4

The review of cost-effectiveness studies appears to be identical to that reported for the full trial sample population (patients who have received at least one prior therapy) of PANORAMA-1 trial and therefore does not relate solely to the restricted population which is the focus of the de novo cost-effectiveness analysis reported in their subgroup analysis considering patients who had at least two prior lines of treatment including an IMiD and a BTZ based regimen (Appendix 17). As in their economic analysis for the full trial sample population, it is stated that the structure of the model constructed by Novartis was informed by the review. It is worth noting, therefore, that, while BTZ as monotherapy or in combination with DEX appears as a comparator in a number of studies in the literature, the only comparator against which PANO was assessed for the restricted population was LEN/DEX.

6.1.2. Novartis' economic model submitted to NICE

We now turn to the economic evaluation that Novartis presented to NICE. This section solely applies to the economic analysis is presented for the subgroup of patients with relapsed or relapsed and refractory MM who had at least two prior lines of treatment including an IMiD and a BTZ based regimen.

The model was built in Microsoft Excel©. Here, we summarise the main features of the model.

6.1.2.1. Population

In this appendix the economic analysis is presented for patients with relapsed or relapsed and refractory MM who had at least two prior lines of treatment including an IMiD and a BTZ based regimen. In the absence of head-to-head trial between PANO/BTZ/DEX and LEN/DEX, the relative effectiveness estimates were derived from a comparison of outcomes for the former regimen's arm in PANORAMA-1 trial and pooled outcome data of the latter regimen's arms in the MM-009 and MM-010 trials, for the patient subgroup. The company highlight the substantial difference in prior treatments of MM-009/MM-010 trial patients compared with any of the PANORAMA-1 patients. Novartis state that 188 patients (from total of 387 in PANO/BTZ/DEX patients PANORAMA-1 trial), have received 2 to 3 lines of treatment. This figure is consistent with San-Miguel et al.[126], although Table 10 of the full PANORAMA-1 trial sample analysis makes a reference to 189 patients. Novartis present the patient characteristics in Table 3 of their subgroup analysis. The percentage of patients who are relapsed or relapsed and refractory in the full trial sample have been transposed. The figures should be as follows:

[125] Celgene. NICE Single Technology Appraisal (STA) - Pomalidomide for relapsed and refractory multiple myeloma. June 2014.

[126] San-Miguel JF, Hungria VT, Yoon SS et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15:1195–206.

- Relapsed and refractory: 35% representing 134 patients of 387;
- Relapsed: 64% representing 247 patients of 387;

This table is replicated with the correct figures below.

In table 10 of the full PANORAMA-1 trial sample analysis, 6 patients out of 387 receiving PANO/BTZ/DEX have been reported as other (neither relapsed and refractory nor relapsed).[127] These are excluded from the table below.

Table 60: Patient characteristics within PANORAMA-1 trial

Parameter	*PANO/BTZ/DEX*	
N	*387*	*73*
Population	*ITT*	*Prior IMiD and BTZ and ≥ 2 prior LoT*
Baseline age, median (range)	*63 (28 to 84)*	*60 (33 to 79)*
*Male, N (%)**	*52.2%*	*33 (45.2%)*
ECOG performance status, n (%) *0* *1* *2+*	 *45.2%* *49.4%* *4.9%*	 *41 (56.1%)* *30 (41.1%)* *2 (2.7%)*
MM characteristic, n (%) *Relapsed & refractory* *Relapsed*	 **35%** **64%**	 *34 (46.6%)* *39 (53.4%)*
Time since diagnosis (months), median (range)	*37.1 (2.4 to 1275)*	*53.1 (11.6 to 164.8)*

BTZ, bortezomib; DEX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory drug; ITT, Intention-to-treat; LoT, lines of treatment; MM, multiple myeloma; PANO, panobinostat.

Source: Novartis submission, Appendix 17 Table 3

Following the review of the pharmacoeconomic models, a partitioned survived model was considered most appropriate. The company justify the use of this method on the basis of the following considerations:

This model is consistent with the previous models and consists of three key health states:

1. Pre-progression, on treatment;
2. Pre-progression, off treatment;
3. Post-progression.

A partitioned survival model was preferred over Microsimulation models due to:

1. Transparency;
2. Reproducibility; and
3. Tractability.

[127] San-Miguel JF, Hungria VT, Yoon SS et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15:1195–206.

The model allows the clinical benefits of PANO/BTZ/DEX to be captured in terms of TFI and PFS within the targeted patients segment.

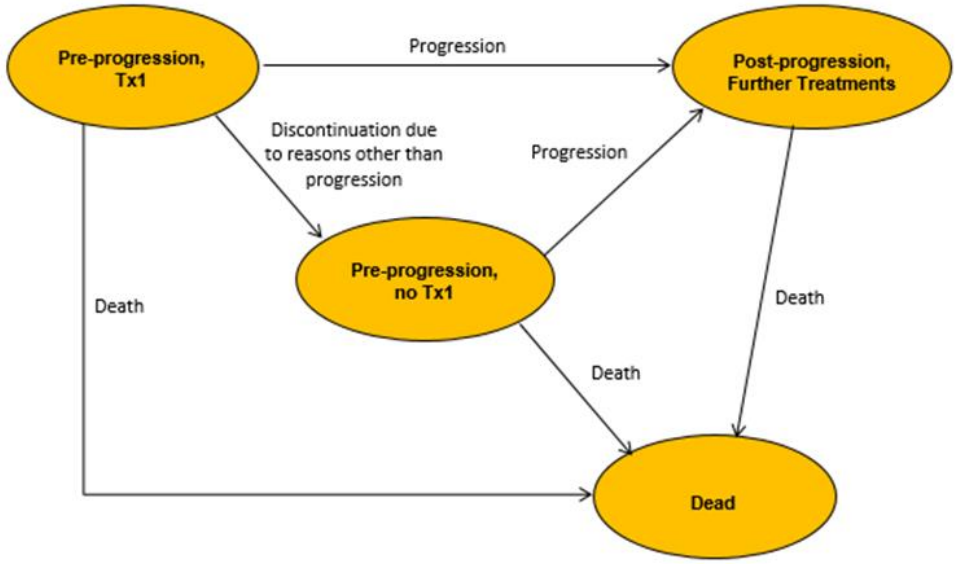
Results of indirect comparisons can be incorporated in the model.

6.1.2.2. Model structure

Novartis developed a decision analytic partitioned survival model. The structure of the model, illustrated in Figure 28, includes two pre-progression health states, one post-progression health state and finally the death health state. The model is reported to capture the three key aspects of MM that are affected by disease progression and the effects of treatment, namely survival, HRQL and costs. Although the model reportedly consists of three key health states, the submission describes four health states:

- Health state: pre-progression, on treatment (Tx1);
- Health state: pre-progression, no treatment (no Tx1);
- Health state: post-progression, last line of treatment (LLoT);
- Health state: death.

Figure 28: Structure of the decision analytic partitioned survival model



Note: Treatment 1 (Tx1) in the health economic model structure does not refer to the first treatment of newly diagnosed MM patients or does not represent the absence of any prior treatment for MM.

Source: Novartis submission, Appendix 17 Figure 1

The company made the assumptions that following PANO/BTZ/DEX treatment, patients would move to LLoT.

A single survival curve was applied to inform the risk of death while in post-progression.

Novartis opted to add POM/DEX in the LLoT packages instead of LEN/DEX as they claim that "*there is no evidence to support the replacement of POM/DEX with LEN/DEX in the UK treatment pathway*".

All patients enter the model in the pre-progression health state Tx1 and receive either PANO/BTZ/DEX or LEN/DEX. Patients progress by moving from the two pre-progression health states, Tx1 and no Tx1, to the post-progression health state (LLoT).

Patients in the Pre progression Tx1 health state are subject to:

- early discontinuation due to progression or relapse ; patients move to post-progression;
- discontinuation for any other reasons than progression or relapse; patients move to Pre-progression, noTx1;
- discontinuation due to treatment completion (16 cycles = 48 weeks).

Patients in the Pre progression no Tx1 health state are subject to:

- progression; or
- death.

Patients in the Post progression health state are assumed to receive post-progression treatment until death. A mix of various therapies is considered in this health state.

Patients are at risk of dying at any time therefore they can move to this health state from any other health state.

The key features of the analysis is presented in the table below.

Table 61: Key features of analysis

Factor	Chosen value	Justification	Flexibility	Reference
Time horizon	*25 years*	*Appropriate timescale for evaluating conditions with high death rates such as rrMM, to enable capturing (differential) costs and outcomes*	*Flexibility includes time horizons ranging from "trial period" to 25 years*	*Guide to the methods of technology appraisals*[128]
Cycle length	*3 weeks*	*Reflects the drug administration schedule in the PANORAMA-1 trial*	*Fixed**	*San Miguel et al, 2014*[10]
Half-cycle correction	*Applied*	*Consistent with previous economic models and the NICE Guide to the methods of technology appraisals*	*Fixed*	*NICE technology appraisals for BTZ,*[129] *LEN*[130] *and POM*[131]*; Guide to the methods of technology appraisals*[132]
Were health effects measured in QALYs; if not, what was used?	*Life years (Lys) and quality-adjusted life years (QALYs)*	*Consistent with previous economic models and the NICE Guide to the methods of technology appraisals*	*Outcomes such as "Life years gained" and "Time spent off-treatment" are presented*	*NICE technology appraisals for BTZ, LEN and POM Guide to the methods of technology appraisals*[133]
Discounting	*Effects: 3.5%* *Costs: 3.5%*	*Consistent with the NICE Guide to the methods of technology appraisals*	*Flexible: any values can be implemented*	*Guide to the methods of technology appraisals*[134]
Analysis perspective	*Healthcare system (NHS/PSS)*	*Consistent with the NICE Guide to the methods of technology appraisals*	*Direct costs are included, Option to include indirect costs*	*Guide to the methods of technology appraisals*[135]

* The different cycle length for lenalidomide and pomalidomide has been accounted for in all cost calculations

Source: Novartis submission, Appendix 17 Table 5

6.1.2.3. Treatment effectiveness within submission

Treatment effectiveness within the model works essentially through transition probabilities between the health states as presented in section 5.1.2.2. In the PANO/BTZ/DEX arm of the model, transition probabilities were derived from survival functions based primarily on patient-level data from the

[128] National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Available from: http://www.nice.org.uk/article/pmg9/chapter/Foreword (Accessed 12 March 2015).

[129] National Institute for Health and Care Excellence. Technology Appraisal 228: Bortezomib and thalidomide for the first-line treatment of multiple myeloma. July 2011. Available from: https://www.nice.org.uk/guidance/ta228. (Accessed 5 June 2014).

[130] National Institute for Health and Care Excellence. Technology Appraisal 171: Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. June 2009. Available fromt: http://www.nice.org.uk/TA171. (Accessed 4 October 2013).

[131] Celgene. NICE Single Technology Appraisal (STA) - Pomalidomide for relapsed and refractory multiple myeloma. June 2014.

[132] National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Available from: http://www.nice.org.uk/article/pmg9/chapter/Foreword (Accessed 12 March 2015).

[133] National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Available from: http://www.nice.org.uk/article/pmg9/chapter/Foreword (Accessed 12 March 2015).

[134] National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Available from: http://www.nice.org.uk/article/pmg9/chapter/Foreword (Accessed 12 March 2015).

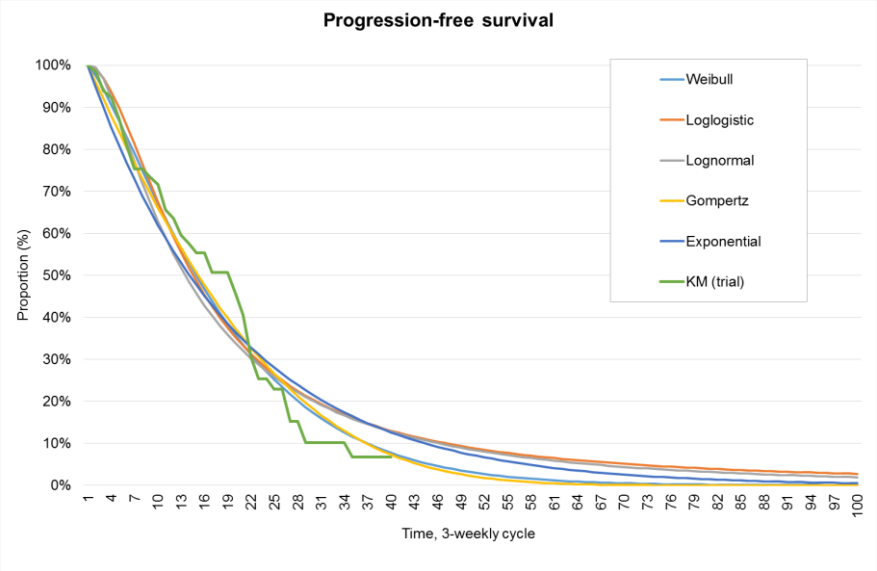
[135] National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Available from: http://www.nice.org.uk/article/pmg9/chapter/Foreword (Accessed 12 March 2015).

PANORAMA-1 trial. Parametric survival curves were fitted to Kaplan-Meier curves on the subgroup of 73 patients in the PANO/BTZ/DEX group receiving at least two prior lines of treatment including an IMiD and BTZ to estimate the risk of progression or pre-progression death (PFS), risk of treatment discontinuation and risk of death. For patients receiving LEN/DEX in the model, the transition probabilities were generated by applying HRs estimated by indirect comparisons methods (as described in section 4.10 of the Novartis submission) to transition probabilities of PANO/BTZ/DEX.

Compared with the analysis of the full PANORAMA-1 trial sample model, the subgroup population model departs from the two stage process of modelling PFS, whereby a logistic regression was used to model the probability of progression relative to PFS events. In this model, a mortality rate is applied directly to the patients who are either on treatment, or alive and off treatment, and who are progression free. It was assumed that, after PANO/BTZ/DEX treatment, patients would be at risk of progressing to LLoT, or patients would discontinue PANO/BTZ/DEX due to reasons other than progression or due to treatment progression. Once patients enter the post-progression health state (LLoT), they receive post-progression treatment until death, with no further progression or transition between treatments possible. Post-progression treatment i.e. 3rd and 4th line consists of a mix of various therapies such as POM or LEN/DEX treatments.

For patients receiving PANO/BTZ/DEX, the five survival models were fitted to the Kaplan-Meier curves for PFS and OS in the subpopulation. On the basis of the AIC and BIC statistics and visual inspection, the Weibull model was selected as the best fit for PFS in the subpopulation. It was difficult to discriminate between the Weibull and Gompertz distributions, the latter being selected as the best fit for OS. Figure 29 below show the 5 different parametric curves and the Kaplan Meier curve for PFS.

Figure 29: PFS Kaplan–Meier curve and fitted parametric models for the population with prior IMiD and BTZ and ≥ 2 prior lines of treatment



Source: Novartis submission, Appendix 17 Figure 2

The indirect treatment comparisons generated estimates of HRs for PFS and OS between LEN/DEX and PANO/BTZ/DEX. HRs were estimated for the full trial population as well as subpopulations receiving two or three prior lines of treatment. This gave seven scenarios comparing PFS and OS of LEN/DEX vs. PANO/BTZ/DEX (four sets of results for an equal number of different indirect comparison methods

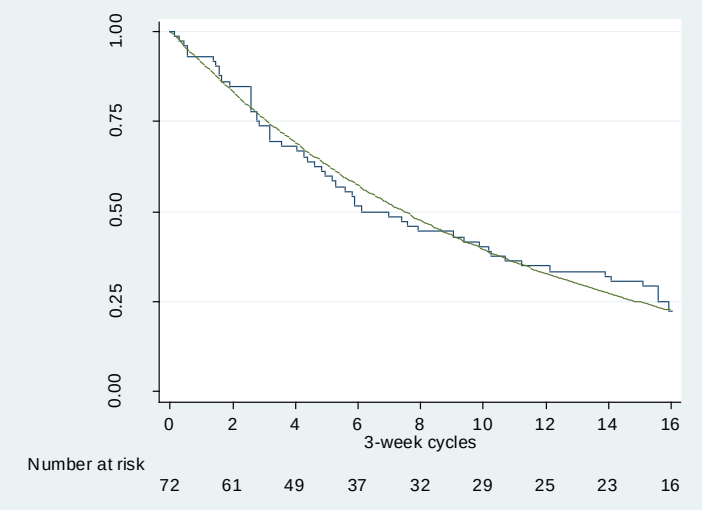
applied to the full trial sample and three to the subpopulation with two or three prior lines of treatment). It was assumed that these HRs were applicable to the subgroup under investigation (the subpopulation with at least two prior lines of treatment including IMiD and BTZ). It was not clear to the ERG why the submission had considered the set of results for the full trial sample in the PANO/BTZ/DEX arm of PANORAMA-1, in addition to the results for the subpopulation in their subgroup analysis rather than the three sets of results for the subpopulation of 2-3 prior regimens alone, nor how population with at least one prior line of treatment results should be interpreted in the context of the full trial sample results presented in the full trial sample analysis.

The transition probabilities for risk of treatment discontinuation were derived in the same way as for the risk of progression or pre-progression death. The same five parametric survival models were fitted to treatment discontinuation data from the PANORAMA-1 trial using the safety analysis set of patients (72 patients). Subsequently, AIC and BIC values are provided to justify the use of the exponential distribution to be the best fitting model amongst the five tested for discontinuation while on PANO/BTZ/DEX. The exponential model was considered the best model for BTZ/DEX responders. The Kaplan-Meier plots and fitted models are reported in Source: Novartis submission, Appendix 17 Figure 5

Figure 33 below.

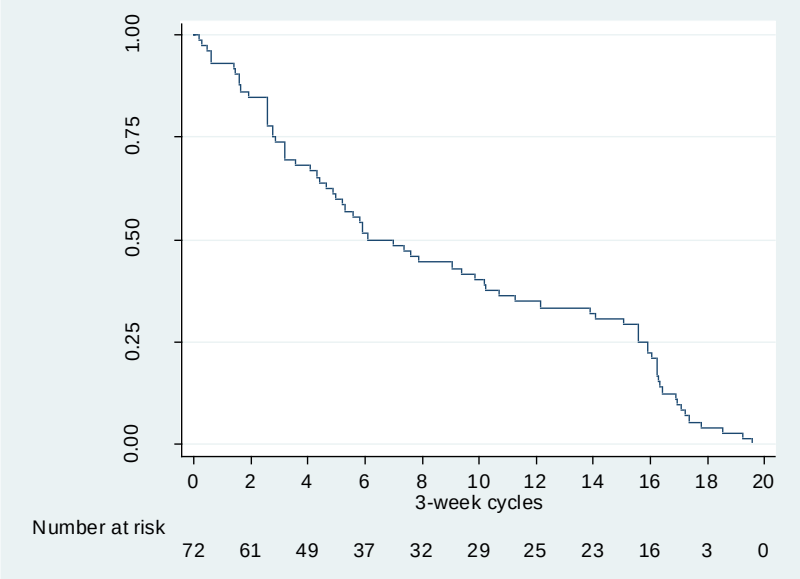
Figure 30: Proportion of patients without treatment discontinuation: subpopulation with prior IMiD and BTZ and ≥ 2 prior lines of treatment: a) Kaplan-Meier curve and fitted parametric models (PANO/BTZ/DEX – exponential model) for 48 weeks b) Kaplan–Meier curve presenting full follow-up data

d) PANO/BTZ/DEX – exponential model (48 weeks)



Source: Appendix Figure 4a)

e) PANO/BTZ/DEX – full follow up data



BTZ, bortezomib; DEX, dexamethasone; IMiD, immunomodulatory drug; PANO, panobinostat.
Source: Appendix Figure 4 a) and 4 b)

For the LEN/DEX group, unlike PFS and OS, treatment discontinuation cannot be compared between the two treatment regimens using hazard treatment comparisons because LEN/DEX is a continuous treatment. Comparing the median PFS and median treatment duration for the PANORAMA-1 full trial population (11.1 and 10.1 months) and the PANORAMA-1 subpopulation with two or three prior lines of treatment (9.5 and 9.2 months), it was assumed that the risk of treatment discontinuation for the full trial sample is 9.9% higher (11.1/10.1) than the risk of PFS in each model cycle and 3.3% higher (9.5/9.2) in the subpopulation.

Error! Reference source not found. below summarises the approaches used to derived transition probabilities and their use in the model.

Table 62: Approaches used to derived transition probabilities and their use in the economic model

Parameter	*Data source*	*Model used for base case*	*Use of transition probabilities*
PANO/BTZ/DEX			
Risk of progression or death	*PANORAMA-1, PANO/BTZ/DEX arm Patient-level PFS data*	*Weibull*	*Pre-progression, Tx1, PANO/BTZ/DEX*
Risk of treatment discontinuation	*PANORAMA-1, PANO/BTZ/DEX arm Patient-level treatment duration data*	*Exponential*	*Pre-progression, Tx1, PANO/BTZ/DEX*
Risk of death	*PANORAMA-1, PANO/BTZ/DEX arm Patient-level OS data*	*Gompertz*	*Post-progression (derived as OS-PFS) PANO/BTZ/DEX*
Risk of experiencing adverse events	*PANORAMA-1, PANO/BTZ/DEX arm Patient-level AE data*	*Occurrence probability*	*Pre-progression, Tx1, PANO/BTZ/DEX*
LEN/DEX[a]			
Risk of progression or pre-progression death (relative to	*Simulated patient level data from MM-009/010, published Kaplan–Meier*	*Hazard ratio*	*Pre-progression, Tx1, LEN/DEX*

Parameter	Data source	Model used for base case	Use of transition probabilities
PANO/BTZ/DEX)	*plot for PFS*		
Risk of treatment discontinuation	*Median PFS and median treatment duration published for MM-009/010*	*Hazard ratio*	*Pre-progression, Tx1 PANO/BTZ/DEX*
Risk of death (relative to PANO/BTZ/DEX)	*Simulated patient level data from MM-009/010, published Kaplan–Meier plot for PFS*	*Hazard ratio*	*Post-progression, Tx1 (derived as OS-PFS) LEN/DEX*

[a] For LEN/DEX, to keep the model parsimonious, exponential distribution was applied.

AE, adverse event; BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; Tx, treatment.

San Miguel et al. 2013[136], Dimopoulos et al 2009[137], Stadtmauer et al 2009[138]

Source: Novartis submission, Appendix 17 Table 6

For OS, the Kaplan-Meier curves and the fitted Gompertz distribution for PANO/BTZ/DEX patients in the subgroup of ≥2 prior therapies did not display the divergence between the actual and predicted outcomes observed for the full PANORAMA-1 trial sample, as shown in Figure 34 (compare this with Figure 26). In the subgroup analysis, the model underestimates PFS compared with the clinical trial results for patients people who have received at least 2 previous treatments including an IMiD and BTZ receiving PANO/BTZ/DEX (12 months vs. 12.5 months). Modelled OS is also underestimated compared with the clinical trial (20.2 months vs. [redacted] months). Median OS derived from the model of 26.2 months or 2.18 years compares with mean survival of 2.29 years or 27.46 months. The median survival figures are presented in Table 72 of this report. As PFS and OS for LEN/DEX were derived from the indirect treatment comparison, it was not possible to compare the Kaplan-Meier curves with the modelled data. Median survival was not reported for patients receiving LEN/DEX, while mean survival was 2.22 years derived from the full trial population data using MAIC approach. The mean survival based on Unadjusted Cox method using the subpopulation data was 2.19 years. Details of the MAIC and Unadjusted Cox approaches for indirect treatment comparisons are given in Section 4.3 of this report.

[136] San Miguel J, Weisel K, Moreau P et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. The Lancet oncology 2013;14:1055–66.

[137] Dimopoulos MA, Chen C, Spencer A et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia 2009;23:2147–52.

[138] Stadtmauer EA, Weber DM, Niesvizky R et al. Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma. Eur J Haematol 2009;82:426–32.

Figure 31: Kaplan–Meier curve and modelled OS: people who have had at least 2 previous treatments including an IMiD and BTZ

Source: Model

6.1.2.4. Health related quality of life

Health related quality of life was assessed using a mapping approach (as used for the full trial sample analysis described in Section 5.1.2.3) combined with evidence from the literature. Mean and median utility values for the PANO/BTZ/DEX patients, based on the data collected in PANORAMA-1, were 0.679 and 0.696. The submission reports that the subgroup analysis used, correctly, mean values instead of median values. As no preference based utility data was available for LEN/DEX treatment in the subpopulation being examined in the analysis presented in Appendix 17 of the submission, two scenarios were explored. In the first, the utility value for LEN/DEX patients was assumed to be equal to BTZ/DEX and, in the second, it was assumed to be the same as that associated with the progression-free no treatment health state. The utility value used for the progression-free no treatment health state is 0.720 and is coming from the the published value associated with the treament-free interval from Acaster et al. 2013). The first scenario was applied for the base case, therefore the utility value of the pre-progression health state in PANO/BTZ/DEX patients was of 0.679 and 0.716 for pre-progression, on treatment health state in LEN/DEX.

The analysis referred to the literature for the pre-progression, no treatment health state (state B) and the post-progression health states C and D (LLoT). The utility of health state B was set to 0.72 based on Acaster et al. (2013) while the utility of states C and D was set to 0.64 based on van Agthoven et al. (2004).

As with the analysis of patients who have received at least one prior therapy, for the subgroup analysis the company state that the mapped overall mean value was used for the pre-progression on treatment health state for PANO/BTZ/DEX arm, as described in Section **Error! Reference source not**

found.Error! Reference source not found.. Using the health state-specific utilities and data on time spent in each health state in the two treatment groups, average utility values were obtained for PANO/BTZ/DEX and LEN/DEX groups, respectively.

Utility values used for the indirect treatment comparison are presented in the table below.

Table 63: Utility values by state

Health state	Utility (SD) n = 4172[a]
A: Pre-progression, Tx1 (PANO/BTZ/DEX)	0.679 (0.182)
A : Pre-progression, Tx1 (LEN/DEX)	0.716 (0.201)
B: Pre-progression, No Tx1	0.720 (0.200)
C and D: Post-progression, (LLoT)	0.64 (0.1289)
Dead	0

Source: Adapted from Novartis submission, Appendix 17 Table 15

6.1.2.5. AEs

No search was conducted for evidence on AEs. Novartis estimated the occurrence of AE associated with PANO/BTZ/DEX arm based on the AEs reported in the PANORAMA-1 trial.

Novartis present the table of AEs as observed in people who have had at least 2 previous treatments including an IMiD and BTZ receiving PANO/BTZ/DEX. Daily AE rates for these patients were converted into 3-weekly occurrence rates and then transformed into 3-weekly probabilities.

Table 64: AEs observed in the prior IMiD and prior BTZ and ≥ 2 prior lines of treatment trial population (safety set)*

PANO/BTZ/DEX (n = 72)		
Mean study treatment exposure, days	*180.7*	
Total exposure time to treatment, patient-days	*13,008*	
Grade ¾ AEs	*N*	*3-weekly occurrence probability*
Anaemia	*16*	*0.025*
Asthenia	*6*	*0.010*
Diarrhoea	*24*	*0.038*
Fatigue	*16*	*0.025*
Hypokalaemia	*15*	*0.024*
Hyponatraemia	*5*	*0.008*
Lymphopenia	*9*	*0.014*
Neutropenia	*23*	*0.036*
Pneumonia	*10*	*0.016*
Thrombocytopenia	*43*	*0.067*

AEs, adverse events; BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

* Safety set = patients who received at least one dose of study treatment

Source: Novartis submission, Appendix Table 22

No number of AEs or probabilities of occurrence are presented in the report and model for LEN/DEX.

The cost of management of AE per cycle was estimated at £136.85 for PANO/BTZ/DEX. The cost for LEN/DEX was directly taken from NICE TA171[139] and converted to a 3-weekly AE cost of £12.83.

The table of cost per AE was presented in Section 5.1.2.4.

6.1.2.6. Resources and costs

The model submitted by Novartis for the subgroup analysis used costs based on the NHS & personal social services (PSS) perspective. Novartis clarified that PSS perspective "*was considered but no particular aspects were identified for inclusion*". Costs included in the model are drug costs and disease management costs (such as monitoring costs, administration costs and outpatient visits) and AE costs.

AEs were costed using NHS reference costs and previous TAs. Other miscellaneous costs were considered in the economic analysis. This included the cost of terminal care.

Estimates of resource use were obtained from literature searches and previous guidelines. The summary table of health care costs is presented below.

Table 65: Healthcare costs

Health states	Items	Value
Pre-progression, Tx1	*PANO/BTZ/DEX*[a]	*£5,366 (first treatment phase, cycles 1 to 8)* *£4,562 (second treatment phase, cycles 9 to 16)*
	LEN/DEX	*£2,831.69*
	Concomitant med. To LEN/DEX	*£95.20*
	IV administration	*£156*
	Monitoring and tests	*£185.56*
	Adverse events	*PANO/BTZ/DEX: £136.85*
	Total (PANO/BTZ/DEX)	*£6,293 (cycle 1 to 8)* *£5,176 (cycle 9 to 16)*
	Total (LEN/DEX)	*£2,926.89*
Pre-progression, no Tx1	*Monitoring costs*	*£185.56 / 2 = £92.78*
Post-progression other treatments	*POM/DEX* *Concomitant med.*	*£6098.63* *£67.89*
	Other active treatments	*£1,001*
	MRU	*£2,188*
Death	*Terminal care*	*£1,235 lump sum applied on death*

[a] Based on assumption.

[139] National Institute for Health and Care Excellence. Technology Appraisal 171: Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. June 2009. Available from: http://www.nice.org.uk/TA171. (Accessed 4 October 2013).

BTZ, bortezomib; DEX, dexamethasone; IV, intravenous; LEN, lenalidomide; MRU, medical-resource utilisation; PANO, panobinostat; POM, pomalidomide.
Source: Novartis submission, Appendix 17 Table 21

The following NHS costs were included in the analysis:

- Drug acquisition costs (including administration costs for BTZ);
- Treatment monitoring costs;
- Costs for the management of AEs;
- Terminal care costs.

Drug acquisition costs

Apart from the assumed price of PANO, which was set at £776, drug acquisition costs based on the most recent available list price (BNF) were used. Testing costs were drawn from the national schedule of reference costs and other published sources. The costs of managing AEs were based on recent NICE oncology submissions while terminal care costs were obtained from the National Audit Office publication 'End of life care'[140] and attached to each death occurring in the model.

BTZ is dosed per body surface area. The surface area was estimated at 1.81m^2 by utilising average body weight and height of the PANORAMA-1 trial sample. This cost is stated to correspond to the average body surface area of 1.82m^2 (page 38). However as per model, the figures presented below, correspond to average body surface area of 1.81m^2. Novartis clarified that the figure of 1.82m^2 should be amended to 1.81m^2 both in the submission (but does not point out all sections where it should be corrected, such as page 48 of the Appendix 17) and in the model. The table below corresponds to average body surface area of 1.81m^2.

Table 66: Unit cost and cost per administration for each drug

Drug	Unit	Unit cost	Dose	Cost/ dose	Source
*Panobinostat**	*20 mg*	*£776.00*	*20 mg*	*£776.00*	*Assumption*
Bortezomib	*3.5 mg*	*£762.38*	*1.3 mg/m^2*	*£512.54*	*BNF*
Dexamethasone	*2 mg*	*£0.78*	*20/40 mg*	*£7.80/ £15.6*	*BNF*
Lenalidomide	*25 mg*	*£208.00*	*25 mg*	*£208.00*	*BNF*
Doxorubicin	*30 ml*	*£18.72*	*30 mg/m^2*	*£102.21*	*BNF*
Thalidomide	*200 mg*	*£42.64*	*200 mg*	*£42.64*	*BNF*
Cyclophosphamide	*50 mg/300 mg*	*£0.82/£4.92*	*50 mg/300 mg*	*£0.82/£4.92*	*BNF*
Pomalidomide	*4 mg*	*£423.00*	*4 mg*	*£423.00*	*BNF*

BNF, British National Formulary; [a] panobinostat price is based on assumption
Source: Novartis submission, Appendix 17 Table 16

As PANO/BTZ/DEX and LEN/DEX regimens are given as 3-week cycles, Novartis present the cost per 3-week cycle. In response to a clarification question regarding minor differences in cost estimates presented in Table 21 of the Appendix 17 of the submission and those presented in the text in Section 1.5.2 of the Appendix 17 of the submission, Novartis confirmed that the costs per 3-week cycle for PANO/BTZ/DEX and LEN/DEX should be as reported in Table 21 of the Appendix 17 of the submission

[140] National Audit Office. End of life care. 2008. Available at: http://www.nao.org.uk/wp-content/uploads/2008/11/07081043.pdf (Accessed: 14 January 2014)

(or as Table 65 in this report). Thus the cost of PANO/BTZ/DEX in cycles 1-8 should be £5,366 per cycle and £4,462 per cycle in cycles 9-16. The costs of PANO/BTZ/DEX and LEN/DEX take account of treatment interruptions and dose reductions permitted in PANORAMA-1. Due to these factors, dose intensities of PANO, BTZ and DEX among PANO/BTZ/DEX patients were estimated to be 76.3%, 74.0% and 79.8% for the subgroup of ≥2 prior lines of therapy, while dose intensity of LEN and DEX in LEN/DEX patients were not presented. These updated figures were reported in the clarifications presented by Novartis and have a significant impact on the ICER originally submitted. This is further discussed in Section 7 of this report.

It was assumed that BTZ is administered intravenously in all patients as in the PANORAMA-1 study. The cost of this was set to the adult follow-up outpatient mandatory tariff price for the Haematology speciality from the 2013-14 UK National Tariff. Other drugs are assumed to be administered orally and therefore to involve no administration cost. Subcutaneous administration was assumed to be £25.00 as per cost of a nurse visit (no reference is given). The result of the analysis based on subcutaneous administration of BTZ was provided during the clarification stage.

The cost of POM, used as 3rd or 4th line of treatment, was also transformed into 3-week cycle cost of £6,097. It was used in combination with DEX, concomitant use of granulocyte colony-stimulating factor (G-CSF) and cost of best supportive care. Treatment cost for LLoT from Gooding et al. 2013[141] was used. This was discussed in Section 5.1.2.5**Error! Reference source not found.**.

There were a number of errors in the initial submission. Novartis corrected them in during the clarification stage. As stated by the company, the errors in the model, such as dose intensity, BTZ underestimation of the administration cost (discussed further) and double counting of IV administration cost have affected the ICER significantly.

Monitoring costs

In the model, monitoring costs were applied to the pre-progression health states (pre-progression on treatment and pre-progression off treatment) but not the post-progression health states. Again, as per Section 5.1.2.5**Error! Reference source not found.**, the values of frequency per cycle are in disagreement with the values used in the model. In the table below the ERG has corrected the values using the ones in the model.

Table 67: Monitoring scheme for pre-progression therapy (PANO/BTZ/DEX or BTZ/DEX)

Activity	*Frequency per cycle*
Serum protein assessment	*1.00*
Skeletal survey (bone X-ray)	***0.06***
Lab results – haematology	*1.00*
Lab results – thyroid function test	***0.23***
Lab results – blood chemistry	*1.00*
Specialist visit	***1.00***

BTZ, bortezomib; DEX, dexamethasone; PANO, panobinostat.

Source: Adapted from Novartis submission, Appendix 17 Table 19 and corrected from the model

[141] Gooding S, Lau I-J, Sheikh M et al. Double refractory myeloma: analysis of clinical outcomes and medical-resource utilisation in a single centre Blood 2013;122:Abstract 1727.

The cost of monitoring was also incorrect. This was, however, corrected during the clarification stage. The cost of monitoring should be £185.56 while on treatment and £92.78 during the TFI.

Treatment monitoring cost of £146 per 3-weekly cycle was calculated from the 4-weekly monitoring cost from NICE TA171[142], which is nor provided in the submission. Novartis do not discuss how they did re-scaling. The unit cost per monitoring activity is already presented in Section 5.1.2.5**Error! Reference source not found.**.

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Miscellaneous costs

The cost of terminal care was also estimated. This is discussed Section 5.1.2.5**Error! Reference source not found.**.

6.1.2.7. Discounting

All costs and health benefits were discounted at a 3.5% rate as recommended by NICE.

6.1.2.8. Sensitivity analysis

A range of deterministic sensitivity analysis was provided in the submission. Deterministic one-way sensitivity analysis was performed on sample variables within the model:

1. HR of the PFS for LEN/DEX;
2. OS Gompertz gamma;
3. Utility of physical functioning - no treatment;
4. Utility of physical functioning - LEN/DEX treatment;
5. HR of OS for LEN/DEX; Note that the Tornado diagrams were mislabelled and the HR of the PFS for LEN/DEX appeared twice. The ERG assume that the one of the labels were for the OS.
6. OS Gompertz constant;
7. Utility of physical functioning - PANO/BTZ/DEX treatment;
8. Discounted Loglog constant;
9. PFS Weibull constant;
10. PFS Weibull p;
11. Utility post-progression_Tx2;
12. HR discounted LEN/DEX;
13. PFS Loglog constant;
14. PFS Loglog gamma;
15. PFS Lognorm constant.
16.

However no tornado diagram was presented as the output of the one-way sensitivity analysis to illustrate the relative influence of uncertain parameters on the model results.

6.1.2.9. Model validation

For the discussion on model validation please refer to Section 5.1.2.8. Additionally, the company mentioned that to reflect UK clinical practice for treating patients in the 3rd or later lines data for patients who had received at least two prior lines of treatment including thalidomide only and BTZ based regimen should be used. This would reduce the poulation size from 73 to 63.

[142] National Institute for Health and Care Excellence. Technology Appraisal 171: Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. June 2009. Available from: http://www.nice.org.uk/TA171. (Accessed 4 October 2013).

The clinical outcomes, however, are relatively similar between the groups as show in the Table 68 below.

Table 68: Clinical data for subgroup populations

Outcome	*Clinical trial result (Prior IMiD, BTZ and ≥ 2 LoT)*	*Clinical trial result (Prior IMiD, BTZ and ≥ 2 LoT including THAL only and BORT)*
Median PFS (PANO/BTZ/DEX)	*12.5 months*	*12.5 months*
Median OS (PANO/BTZ/DEX)	[redacted] *months*	[redacted] *months*
Median treatment duration (PANO/BTZ/DEX)	*4.2 months*	*4.4 months*

Source: Novartis submission, Appendix 17 Table 28

Other limitations are described by Novartis:

- Post-progression treatments have not been reported for LEN/DEX therefore the impact of difference in the post-progression treatments (between PANO/BTZ/DEX vs. LEN/DEX) on survival could not be assessed;
- there was a mismatch between the efficacy data from Dimopoulos et al. 2009[143], Stadtmauer et al. 2009[144] for the combined MM-009/010 trial data, used for the indirect treatment comparisons, and the data used for the treatment costs of LEN/DEX (TA171 NICE Guidance based on the European MM-010 trial only);
- four-weekly cost of LEN/DEX were rescaled to 3-weekly cost, which may also introduce some bias;
- there may be some double counting of terminal care costs as it is not clear from the study of Gooding et al whether end of life care costs were included in their study or not. Novartis claim that because the difference between the OS profiles of the PANO/BTZ/DEX and LEN/DEX is minor, the inclusion or exclusion of terminal care costs has a negligible impact on the results.

6.2. Critique of approach used

6.2.1. Critique of the modelling approach and structure

The structure of the model constructed by Novartis for the subgroup analysis appeared to be logical and had greater clarity than the full trial sample model in terms of the treatment of death and the correspondence between the two arms of the model (PANO/BTZ/DEX and LEN/DEX). The model followed the structure set out in Figure 28**.** The model structure and health states are justified with respect to previous models, including those developed for NICE submissions. The health states

[143] Dimopoulos MA, Chen C, Spencer A et al. Long-term follow-up on overall survival from the MM–009 and MM–010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia 2009;23 2147–52.

[144] Stadtmauer EA, Weber DM, Niesvizky R et al. Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma. Eur J Haematol 2009;82:426–32.

included in the model are the same as in the model presented by Novartis for the analysis of full PANORAMA-1 trial sample with the exception that there is no transition to the state LEN+DEX. Transition probabilities have been estimated using standard methods and the probabilities for the transitions in each time period sum to one.

Key features of the analysis are justified with reference to previous cost-effectiveness models and NICE's guide to the methods of technology appraisals. One aspect of the model design which is not justified is the choice of comparators. While the relevance of LEN/DEX as a comparator for PANO/BTZ/DEX in patients who have received two or three prior lines of therapy including an IMiD and BTZ, the submission does not justify the choice of LEN/DEX as the only comparator in this group of patients. Since this subgroup is represented in PANORAMA-1 and cost-effectiveness analysis draws on the results of the trial for one arm, PANO/BTZ/DEX, it is not clear why it does not draw on results for the other PANORAMA-1 arm, BTZ/DEX, as a relevant comparator in this subgroup as discussed in Section 5.2.3.

Thus, the option of BTZ/DEX was not evaluated alongside PANO/BTZ/DEX and LEN/DEX as a possible therapy in patients who have received two or more prior lines of therapy including an IMiD and BTZ. As a result, it is not possible to compare the cost-effectiveness of PANO/BTZ/DEX and BTZ/DEX in this subgroup and this raises questions about the most appropriate comparator in these patients The interpretation of the cost-effectiveness results should take account of the absence of BTZ/DEX as a comparator in the subgroup cost-effectiveness analysis.

Although the result suggest that the cost per QALY ratio for PANO/BTZ/DEX relative to LEN/DEX exceeds the reference points to which NICE commonly refers of £20,000 per QALY or £50,000 in the case of treatments meeting the end of life criteria (which it is claimed PANO satisfies), the Advisory Committee may wish to know whether LEN/DEX is cost-effective relative to BTZ/DEX in the subpopulation. This question is not straightforward to address given the constraints of the current analysis.

6.2.2. Data input

The critique around data inputs centres on two main issues:

- The definition of the subgroup patient population to which the cost-effectiveness analysis is intended to relate, namely patients who have received two or three prior lines of therapy including an IMiD and BTZ, and the patient group for whom the clinical inputs are relevant, namely patients who have received two or three prior lines of therapy;
- The use of Unadjusted Cox and MAIC method to estimate the HRs for LEN/DEX vs. PANO/BTZ/DEX.

6.2.2.1. Patient group

The cost-effectiveness results generated by the subpopulation model are intended to apply to the following patient group:

- Multiple myeloma patients who have received two or three prior lines of therapy including an IMiD drug and BTZ.

The principal clinical data sources of the cost-effectiveness analysis for this subpopulation are the PANORAMA-1 trials (for PANO/BTZ/DEX) and the MM-009 and MM-010 trials (for LEN/DEX). The Kaplan-Meier and modelled curves for PFS and OS among PANO/BTZ/DEX patients presented in the Appendix 17 of the submission relate specifically to the 73 patients belonging to the two or three prior lines of therapy subgroup enrolled into PANORAMA-1. However, the section dealing with indirect treatment comparisons in the full trial sample analysis (section 4.10.4 of the submission) notes that the study population employed in the comparison, for the naïve, Unadjusted Cox and MAIC approaches, is those with 2 to 3 prior lines of treatment. As reported in Table 30, 142 patients treated with

PANO/BTZ/DEX formed the basis for the MAIC in the subpopulation. These are the 188 patients with 2 to 3 prior lines of treatment excluding those who had previously received LEN (for comparability with LEN/DEX patients as the MM-090/010 trials excluded patients who had received LEN).

The data on which the indirect treatment comparisons were based therefore relate to a broader population than that to which the subgroup population cost-effectiveness analysis is intended to apply. The 142 patients included in Table 30 are further reduced to 137 in the Kaplan-Meier curves presented in **Error! Reference source not found.** and relate to the full trial sample analysis while the numbers receiving PANO/BTZ/DEX and available for the analysis on the subpopulation with 2 to 3 prior lines of treatment is reduced to (an effective sample size of) 22.5 in **Error! Reference source not found.** (after reweighting individual patient level data from PANORAMA-1 to match the baseline characteristics reported in MM-009 and MM010).

6.2.2.2. Mortality data

The modelled survival function for patients in the subpopulation receiving PANO/BTZ/DEX does not appear to diverge from the Kaplan-Meier curves in the way observed for the whole population as shown in **Error! Reference source not found.**. The Gompertz distribution found to provide the best fit to the Kaplan-Meier curves in this group implies an increasing mortality risk and is the most conservative model tested (lies below the others). While Novartis have plotted the fitted overall survival curve for LEN/DEX patients within the model, it has not been compared with the underlying trial data. This would have been useful and feasible given that the Kaplan-Meier curves have been plotted for LEN/DEX patients in Table 26 of the full trial sample analysis report as shown in **Error! Reference source not found.** and **Error! Reference source not found.** of this report.

One concern is that effectiveness data is taken from PANORAMA-1 for the subpopulation with 2 to 3 prior lines of therapy. In contrast, the cost-effectiveness analysis is intended to relate to a subset of this group, that is, those who received two or three prior lines of therapy including an IMiD drug and BTZ. It is unclear therefore whether the effectiveness data included in the subgroup population analysis are appropriate for the patient group of interest (which may be the group of the population in which the positive CHMP opinion for the company's drug has been granted).

As the subgroup analysis indicates, this population model uses hazard ratios (HRs) to link PFS and OS for patients treated with LEN/DEX and those treated with PANO/BTZ/DEX. The reported cost-effectiveness results are based on two methods of indirect treatment comparisons to estimate HRs: Unadjusted Cox regression and MAIC.

In the case of the Unadjusted Cox regression, and as discussed in section 4.3.3.3, the proportional hazards assumption is not consistent with the shape of the Kaplan-Meier curves on PFS and OS for those receiving PANO/BTZ/DEX and LEN/DEX. The crossing pattern of the curves suggests that, in this case, the HR is likely to be an invalid measure of relative effectiveness. Given these reservations, the MAIC approach represents a potentially valid method of obtaining point estimates of relative effectiveness. However, after making the adjustments to the PANORAMA-1 trial data required by the MAIC method, the effective sample sizes were reduced from 314 to 137 in the full trial sample analysis. The implication of this is that some patients were given extremely high weights and that the analysis therefore had correspondingly low power to detect differences (No estimates of uncertainty were

reported by the company). Therefore as already mentioned in Section **Error! Reference source not found.**, MAIC estimates are likely to be unreliable and biased by unobserved confounding.

6.2.2.3. Health related quality of life

The procedure for obtaining utility values in patients treated with PANO/BTZ/DEX in the subgroup population uses the same mapping approach as for the full trial sample (patients who have received at least one prior therapy) analysis. The overall mean for patients receiving PANO/BTZ/DEX was estimated at 0.679 which, as in the full trial sample analysis, the submission states is the figure used for the pre-progression on treatment state. As expected, this value, which applies to patients with more prior treatment regimens received, is somewhat lower than the figure of 0.706 for the whole trial sample population.

In the absence of preference-based utility data for LEN/DEX treatment in the subgroup population, two options were considered. The first option used the utility for BTZ/DEX patients as the appropriate figure for those receiving LEN/DEX, giving a utility of 0.716, also lower than the figure of 0.725 observed for the full PANORAMA-1 trial sample. The second option was to use the utility of the pre-progression, no treatment health state (0.720). This was based on the Acaster et al. 2013[145] utility associated with the TFI. This is a departure from the full trial sample analysis in which the utility of the pre-progression, no treatment health state was assumed to be equal to the mean utility mapped from the last health related quality of life assessment while still on treatment. The ERG have confirmed that the health state-specific utility values reported in the submission and survival times are consistent with the QALY figures presented as part of the cost-effectiveness calculations. Table 69 presents utilities, life years and QALYs by health state.

Table 69: Utility scores, life years and QALYs of the subgroup

	PANO/ BTZ/ DEX	LEN/ DEX	PANO/ BTZ/ DEX	LEN/ DEX	PANO/ BTZ/ DEX	LEN/ DEX
	Life years		Utilities		QALYs – calculated	
Pre-progression Tx1	0.49	0.86	0.679	0.716	0.33	0.62
Pre-progression No Tx1	0.47	0.06	0.72	0.72	0.34	0.04
C+D: post-progression (LLoT)	1.33	1.27	0.64	0.64	0.85	0.81
Total	2.29	2.19			1.521	1.469
Average QoL			0.66	0.67		

Source: Novartis submission, Appendix 17 Table 15 corrected by the ERG

The average utilities in the subgroup population are similar to those in the full trial sample population, with the exception that, in the subgroup population, the comparator (LEN/DEX) has a slightly higher utility (0.67) than PANO/BTZ/DEX (0.66). The small difference in QALYs between the two therapies makes the results difficult to interpret. In the Appendix 17 of the submission, Novartis state, "*the ICERs are volatile and subject to switch from dominant to dominated quite easily*". However, the results of the deterministic sensitivity on the ICER was not presented by Novartis.

[145] Acaster S, Gaugris S, Velikova G, Yong K, Lloyd AJ. Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: a UK cross-sectional survey. Support Care Cancer 2013;21:599–607.

It is worth noting that the utility of LEN/DEX in the pre-progression health state is assumed to be the utility for BTZ/DEX in the subgroup population, once again raising questions about the cost-effectiveness of PANO/BTZ/DEX versus BTZ/DEX in the population who have had at least 2 previous treatments including an IMiD and BTZ. Given the concerns expressed about the method used for the indirect treatment comparison, a direct comparison of the two groups on the basis of PANORMA-1 data would have been a useful additional analysis to carry out.

6.2.2.4. Resources and costs

The resources and the costs used for the PANO/BTZ/DEX arm in the subgroup analysis are identical to the analysis of the patients who have received at least one prior therapy. For the critique of the resources and costs of PANO/BTZ/DEX please refer to Section 5.2.3.5.

The drug acquisition cost of the comparator, LEN/DEX is taken from the BNF. The treatment monitoring costs were taken from NICE TA171,[146] however no detail is provided on the monitoring tests associated with that cost.

Re-scaling was also preformed to acquire the costs for AEs. Again, the costs for LEN/DEX AEs were taken from NICE TA171.

6.2.2.5. AEs

The estimation of the AE occurrence is not well explained in the submission. The ERG cannot verify the figures reported as the number of AEs observed in the safety set of PANORAMA-1 trial sub-set population (**Table 64**).

Expert opinion sought by the ERG confirmed that the safety profile of PANO was a realistic description of the range of side effects seen and corresponds to what is described in the literature both for this drug and other deacetylase inhibitors. However, our expert also pointed out that the cost of AE for Lymphopenia should not be included in the calculation. Removing the cost of Lymphopenia would decrease the cost of AEs for PANO/BTZ/DEX to £134.44 treatment group. The effect of this change, along with other correction carried out in the model will be discussed further in Section 7.

Similarly to the critique of AEs in section, it is not clear why the decrement in utilities associated with the AEs were not taken into account and included in the model.

6.2.3. Sensitivity analysis

A range of sensitivity analyses was provided in Novartis's submission:

- Probabilistic sensitivity analysis (PSA);
- Deterministic sensitivity analysis; and
- Scenario analysis.

These are in depth reviewed in the section below.

6.3. Results included in company's submission

[146] National Institute for Health and Care Excellence. Technology Appraisal 171: Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. June 2009. Available from: http://www.nice.org.uk/TA171. (Accessed 4 October 2013).

This section presents a summary of the results of Novartis' model of the subgroup of patients who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen (the Appendix 17 of the submission).

6.3.1. Deterministic results

6.3.1.1. Base case

Base case inputs of the model are presented in Table 24 of the Appendix 17 of the submission. Table 25 summarises the assumptions the company used. The ERG present Novartis' base case results in the table below. The base case analysis is based on a cost of 20mg capsule of PANO set at £776. The results of the analysis is presented based on relative effectiveness estimates from three statistical methods (Naïve comparison, Unadjusted Cox and MAIC) to estimate the cost-effectiveness results. This set of methods and results is described in section 4.3 of this report. The common comparators method was omitted for the subgroup analysis. Novartis do not present the explanation for excluding the common comparators method. Instead, the company list the advantages of the MAIC and Unadjusted Cox methods.

Furthermore, Novartis state that the two methodologies MAIC and Unadjusted Cox are the most appropriate methods to estimate the relative effectiveness for use in this analysis. In fact the company use MAIC to analyse the full trial sample and Unadjusted Cox to analyse the subpopulation with 2 to 3 prior lines of therapy. No explanation is given on the rationale of using the MAIC and Unadjusted Cox methods. Instead, the company repeat twice in the same section the advantages of the MAIC and Unadjusted Cox method (page and 51 and 52). They claim to present LYs, QALYs and ICERs both for the MAIC and Unadjusted Cox method to "*acquire a fuller picture*" In reality, the MAIC method is applied to the full trial sample only and the Unadjusted Cox to the subpopulation with 2 to 3 prior lines of treatment, with sensitivity analysis performed on the Unadjusted Cox to the subpopulation with 2 to 3 prior lines of treatment only. However, there does not seem to be a logical, systematic method followed by this analyses.

As described earlier in Section **Error! Reference source not found.** it is important to note that the results presented are for the subpopulation 2 to 3 prior lines of therapy, which is not the patient population considered in this economic analysis originally.

As in the full trial sample analysis (described in section 4.3) not many details are presented on the statistical methods. Novartis present the HRs for PFS and OS. The ERG assume that these are the median values, as it not specified in the text. The HR of PFS and OS from the Unadjusted Cox method were incorrect for the PANO/BTZ/DEX arm. These are already presented throughout the report.

Table 70: HRs for LEN/DEX vs. PANO/BTZ/DEX

		PFS		*OS*	
		HR	*SE*	*HR*	*SE*
Full trial population based	*Common comparator method*	*1.870*	*0.356*	*1.216*	*0.384*
	Naïve comparison	*1.081*	*0.216*	*1.006*	*0.201*
	Unadjusted Cox	*0.929*	*0.104*	*0.997*	*0.131*
	MAIC	*1.002*	*0.126*	*1.052*	*0.157*
Based on the	*Naïve*	*1.190*	*0.238*	*0.959*	*0.192*

		PFS		OS	
		HR	SE	HR	SE
subpopulation with 2 to 3 lines of prior treatment	*comparison*				
	Unadjusted Cox	*1.061*	*0.145*	*1.075*	*0.179*
	MAIC	*1.108*	*0.331*	*1.413*	*0.424*

HR, hazard ratio; MAIC, matching adjusted indirect treatment comparison; OS, overall survival; PFS, progression-free survival; SE, standard error.

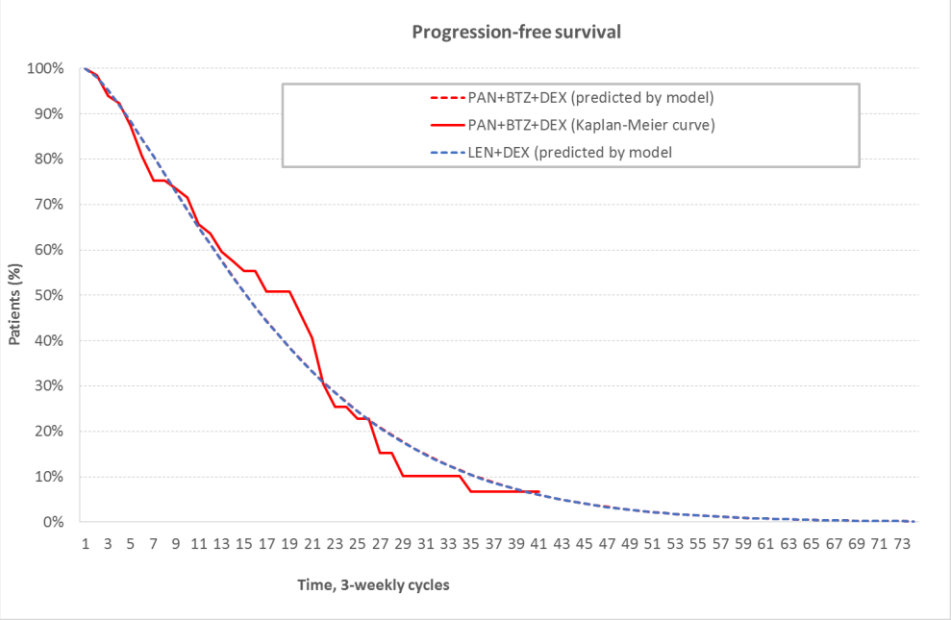
Source: Novartis submission, Appendix 17 Table 26

The company present for both PFS and OS the comparison of the Kaplan-Meier curves with the modelled curves by applying the HR predicted with the MAIC method for the full trial sample and Unadjusted Cox method for the sub population of patients who received 2 to 3 prior lines (reproduced in Source: Novartis submission, Appendix 17 Figure 5

Figure 33). Notably, in the PFS curves for the full trial sample are superimposed since the HR is very close to 1.

Figure 32: a) Progression-free survival and b) overall survival Kaplan–Meier curves derived for LEN/DEX and PANO/BTZ/DEX using the MAIC method for the full patient population

a)



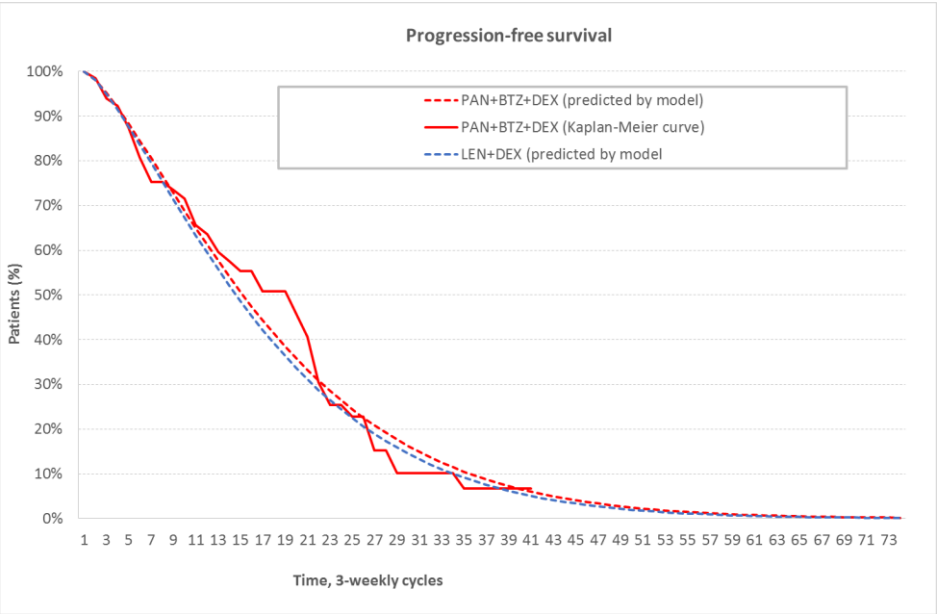
b)

[redacted]

Source: Novartis submission, Appendix 17 Figure 5

Figure 33: a) Progression-free survival and b) overall survival Kaplan–Meier curves derived for LEN/DEX and PANO/BTZ/DEX using the Cox method for the prior 2 to 3 lines of treatment population

a)



b)

BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; PAN(O), panobinostat.
Source: Novartis submission, Appendix 17 Figure 6

The result of MAIC and Unadjusted Cox method show only a small incremental QALY gain of 0.0295 and 0.0518 respectively. As mentioned by Novartis, these "*are not particularly meaningful when considered in real terms"* and therefore the determining factor will be the cost of the PANO/BTZ/DEX combination. "*These small incremental QALYs lead to volatile ICERs thus making interpretation more problematic*". These findings undermine the reliability of the results of the subgroup analysis. This is in addition to the issue raised by the ERG earlier (Section 4.3.3) about the appropriate selection of comparators to answer the decision question of the sub group analysis.

Following the clarification stage, Novartis have updated the base case results using the MAIC and the Unadjusted Cox methods. In these new tables reproduced below in **Error! Reference source not found.**, the company presented base case results for both intravenous and subcutaneous administration of BTZ. In their updated report, Novartis make a reference to the two columns presented in the table below, marking them with "*a*", but fail to attach the information to this note.

Table 71: ICER per the two most plausible methodologies applied (discounted) with the corrected cost calculation and with the updated dose intensity assuming a) intravenous BTZ administration or b) subcutaneous BTZ administration

a) Intravenous BTZ administration assumed

Methodology	*Technologies*	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£) versus LEN/DEX*	*Incremental LYG versus LEN/DEX*	*Incremental QALYs versus LEN/DEX*	*ICER (£) Cost per Lys gained*[a]	*ICER (£) Cost per QALYs gained*[a]
'MAIC' deriving HRs from full trial	*PANO/BTZ/DEX*	£[redacted]	*2.288*	*1.521*	£[redacted]	*0.071*	*0.0295*	£[redacted]	£[redacted]

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
populations	LEN/DEX	£148,567	2.216	1.491					
'Unadjusted Cox' deriving HRs from subpopulation (2 to 3 prior lines)	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.102	0.0518	£[redacted]	£[redacted]
	LEN/DEX	£147,632	2.186	1.469					

b) Subcutaneous BTZ administration assumed:

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
'MAIC' deriving HRs from full trial populations	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.071	0.0295	£[redacted]	£[redacted]
	LEN/DEX	£148,567	2.216	1.491					
'Unadjusted Cox' deriving HRs from subpopulation (2 to 3 prior lines)	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.102	0.0518	£[redacted]	£[redacted]
	LEN/DEX	£147,632	2.186	1.469					

BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; LYG, life years gained; MAIC, matching adjusted indirect treatment comparison; PANO, panobinostat; QALYs, quality-adjusted life years

Source: Clarification questions

Novartis also presented the clinical outcomes of the model. It shows that the model underestimates the PFS by [redacted] months and the OS by [redacted] months compared to the trial outcomes. It also shows that the model overestimates the median treatment duration and hence the cost of PANO/BTZ/DEX. The summary of model results vs. the clinical data is presented in **Table 72** below.

Table 72: Summary of model results vs. the clinical data

Outcome	Clinical trial result (Prior IMiD, BTZ and ≥ 2 LoT)	Model result
Median PFS (PANO/BTZ/DEX)	12.5 months	12.0 months
Median OS (PANO/BTZ/DEX)	[redacted] months	26.2 months
Median treatment duration (PANO/BTZ/DEX)	4.2 months	5.5 months
Proportion of patients experiencing adverse events (PANO/BTZ/DEX)	Rates obtained from trial	Rates obtained from trial

BTZ, bortezomib; DEX, dexamethasone; IMiD, immunomodulatory drug; LoT, line of treatment; OS, overall survival; PANO, panobinostat; PFS, progression-free survival

Source: Novartis submission, Appendix 17 Table 28

The disaggregated PFS and OS results of the MAIC and the Unadjusted Cox methods for the full trial population and the sub population of receiving 2 to 3 prior lines are also presented in the submission in Tables 29 to 33.

6.3.1.2. Deterministic sensitivity analysis

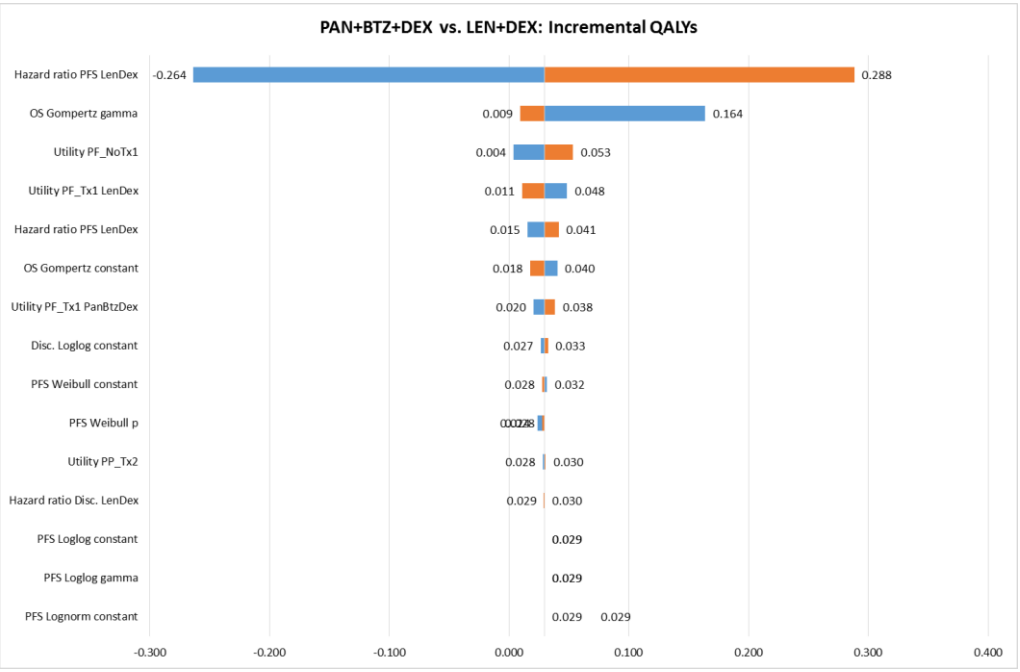
Novartis present the Tornado diagrams for 15 of the most sensitive model parameters and present their impact on:

- Incremental QALYs;
- Incremental costs; and
- ICERs.

It should be noted that the results of the deterministic sensitivity analysis presented for the subgroup analysis have not been updated in light of the changes made during the clarification stage.

It was found that the model outcomes (i.e. QALYs and costs) were most sensitive to the HRs of the PFS and the OS. However, the results presented in the Tornado diagrams showed the PFS HR for LEN/DEX twice. It seems that the OS HR for LEN/DEX has been mislabelled therefore it is impossible to differentiate which one has the most effect on the model outcomes. The Tornado diagrams depicting the impact on incremental QALY gains and incremental costs are reproduced in Figure 34 and Figure 35 below.

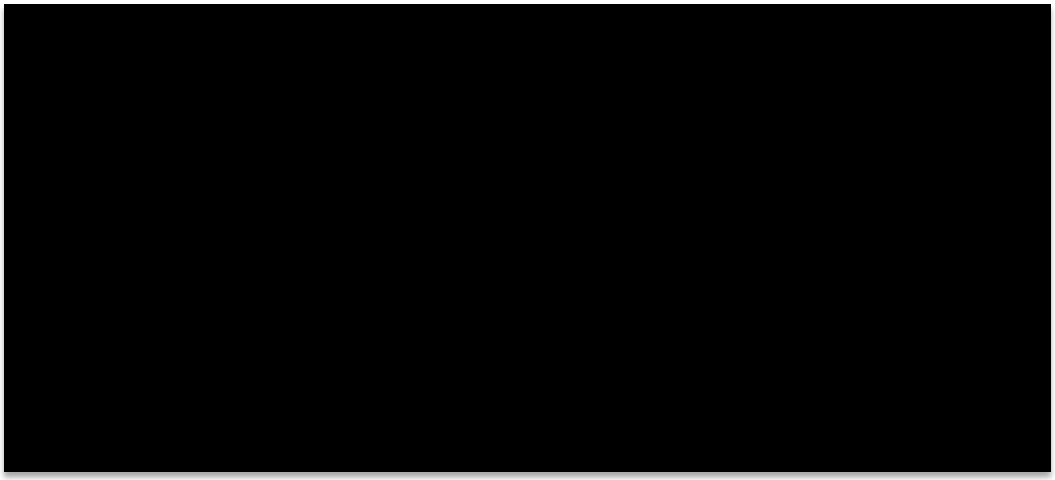
Figure 34: Tornado diagram of incremental QALYs for PANO/BTZ/DEX vs. LEN/DEX using Unadjusted Cox method deriving HRs from data on subpopulation data of 2 to 3 prior lines



BTZ, bortezomib; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; PANO, panobinostat; PFS, progression-free survival; QALY, quality-adjusted life years.

Source: Novartis submission, Appendix 17 Figure 9

Figure 35: Tornado diagram of incremental costs for PANO/BTZ/DEX vs. LEN/DEX assuming both pricing scenarios using Unadjusted Cox method deriving HRs from data on subpopulation data of 2 to 3 prior lines



Source: Novartis submission, Appendix 17 Figure 10

Novartis claim that the relative effectiveness of LEN/DEX vs. PANO/BTZ/DEX influences a lot the model outcomes and this cannot be overcome due to a lack of a clinical data for LEN/DEX population who receive 2 to 3 prior lines of therapy. The company also state that the multiple modelling techniques have been tested to enhance the reliability of the cost-effectiveness calculation. No information on the conclusions derived from the results of these tests has been provided therefore the ERG cannot comment of this claim.

It is mentioned that the model results seem to be more sensitive to the cost of the PANO/BTZ/DEX triple combination treatment, however this parameter has not been varied in the deterministic sensitivity analysis therefore the ERG is not clear on the basis of this statement. However, Novartis noted again that due to the small QALY gains between the two treatments arms, the results are naturally highly sensitive to the cost of the PANO/BTZ/DEX triple combination.

6.3.1.3. Scenario analysis

Here, the ERG list the assumptions of scenario analysis that were made by Novartis in the cost-effectiveness model:

- Discount rate of 5%, rather than 3.5%, was used;
- Time horizons of 5 and 10 years were used instead of 25 years;
- OS was modelled with Kaplan-Meier plus best fitting model instead of Gompertz;
- PFS was modelled with Gompertz rather than Weibull;
- Time to discontinuation was modelled with Kaplan-Meier curves rather than fitted curve;
- Distribution of post-progression treatments: a) equal to the PANORAMA-1 full trial sample and b) equal to prior IMiD population of the PANORAMA-1 trial;
- Utility associated with LEN/DEX (on treatment): in the base case, the utility was equal to the BTZ/DEX arm in PANORAMA-1, whereas in the scenario analysis was set equal to that observed in the off-treatment interval;
- Methodologies generating HRs: instead of the Unadjusted Cox, the following was used:
  - Naïve (ITT);
  - Unadjusted Cox (ITT);

- MAIC (ITT);
- Naïve (2 to 3 prior lines of treatment);

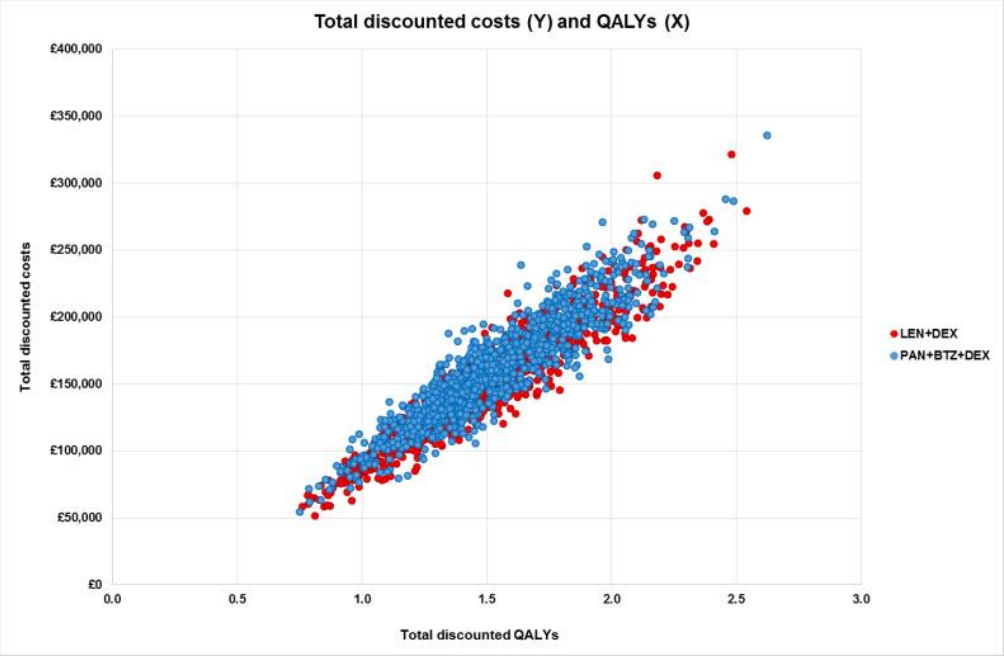
- Threshold analysis for the HR of PFS and PANO price parameters.

The company present a number of tables for the scenario analysis. However, as noted before, some of the model parameters have been changed by Novartis during the clarification stage. Although they provided the updated ICER calculations, Novartis failed to present updated sensitivity analysis results. Due to time constraints, the ERG cannot update these results.

6.3.2. Probabilistic sensitivity analysis results

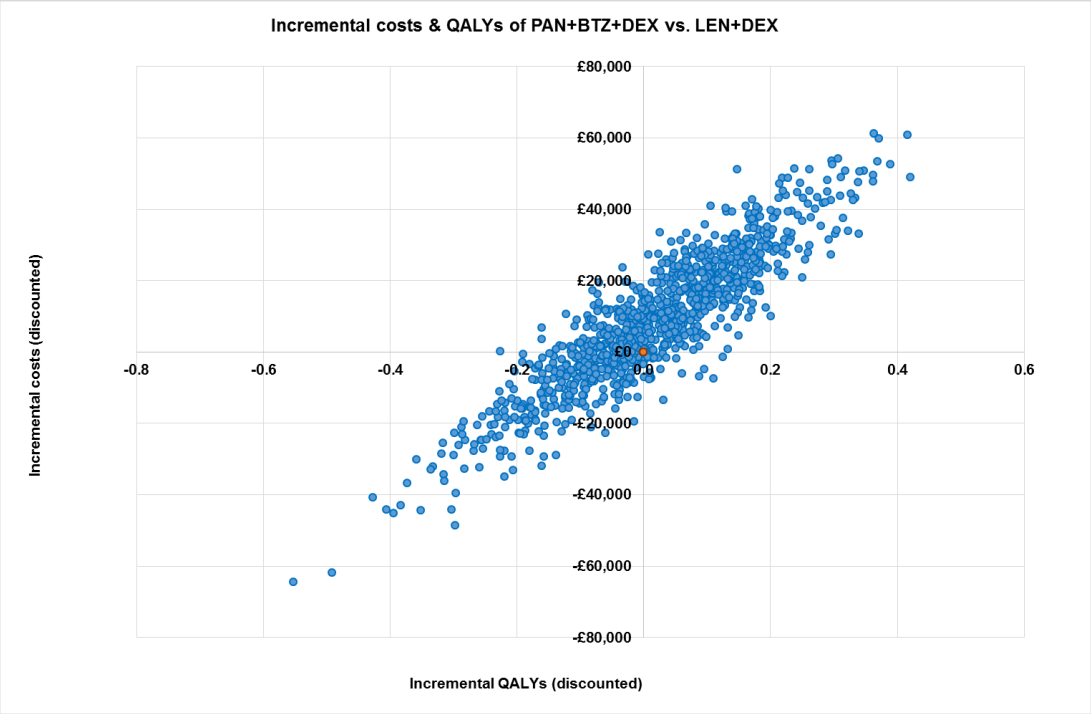
The methods used for the subgroup analysis are similar to the ones used in the full trial sample analysis. It is not clear whether correlation between parameters was taken into account as was claimed for the full trial sample model. Confidence intervals around the model parameters are presented in Table 24 of the Appendix 17 of the submission. Novartis present the scatter plots of simulated total QALY gains and simulated total incremental QALY gains. These scatter plots are presented below. However, as noted before, some of the model parameters have been changed by Novartis during the clarification stage therefore the results of the probabilistic sensitivity analysis presented have not been updated in light of the changes made during the clarification stage.

Figure 36. Scatter plot of simulated total QALYs vs. total costs for PANO/BTZ/DEX and LEN/DEX (probabilistic sensitivity analysis), discounted analysis – using the Unadjusted Cox method and deriving HRs from subpopulation (2 to 3 prior lines) – discounted



Source: Novartis submission, Appendix 17 Figure 7

Figure 37. Simulated total incremental QALYs vs. incremental costs of PANO/BTZ/DEX and LEN/DEX (probabilistic sensitivity analysis), discounted analysis – using the Unadjusted Cox method and deriving HRs from subpopulation (2 to 3 prior lines) – discounted



Source: Novartis Submission, Appendix 17 Figure 8

Novartis found that for the PANO/BTZ/DEX triplet the QALY gains are "*virtually the same*" with the mean incremental QALY gain of 0.044 (CI: -0.32 to 0.34) and the mean incremental cost is higher. The analysis found that price of the triplet therapy drives the likelihood of the cost-effectiveness. "*Because both the simulated incremental QALY and cost outcomes tend to spread around zero, the lower the price of the PANO/BTZ/DEX combination treatment ends up, the higher the likelihood that starting third-line treatment with PANO/BTZ/DEX will result in a 'cost saving' treatment choice*." The results of the analysis is presented below. However, these are likely to be reduced by the parameter change specified in the clarification questionnaire. As already noted before, some of the model parameters have been changed by Novartis during the clarification stage. Though the company provided updated ICER calculations, Novartis failed to present updated sensitivity analysis results. Due to time constraints, the ERG cannot update these figures.

Table 73. Values and 95% confidence intervals around key model outcomes

	Cost	*Mean incremental cost*	*QALYs*	*Incremental QALY*
PANO/BTZ/DEX	*£[redacted] (£[redacted] to £[redacted])*	*£[redacted] (£[redacted] to £[redacted])*	*1.549 (1.045 to 2.142)*	*0.044 (–0.316 to 0.341)*
LEN/DEX	*£151,849 (£79,515 to £249,022)*		*1.505 (0.960 to 2.205)*	

Source: Novartis submission, Appendix 17 Table 36

7. Additional work undertaken by the ERG

7.1. Correction for errors in Novartis' model

In this section we explore the implications of some of the errors found in Novartis' model. However, given the ERG's concerns about methodological issues of the indirect comparison namely the MAIC and the Unadjusted Cox methods to derive the HRs from data on the subpopulation of 2 to 3 prior line of treatments, the findings for the subgroup population of patients who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen should be interpreted with extreme caution.

As the full trial sample analysis refers to the PANORAMA-1 full trial sample comparing PANO/BTZ/DEX with BTZ/DEX among patients who have received at least 1 prior line of therapy, the Appendix 17 of the submission refers to the PANORAMA-1 trial population comparing PANO/BTZ/DEX with LEN/DEX among patients who have received at least 2 lines of prior treatment including IMiD and BTZ. These are potentially separate indications, therefore, the ERG present the corrections firstly for the full trial population analysis and secondly for the subgroup analysis.

7.2. Additional searches

The ERG undertook searches in trials registries to identify any additional trials. The scoping searches were also undertaken to explore the omission of the brand name 'Farydak' from the efficacy searches.

7.3. Correction for errors in Novartis' models

Due to time constraints, the ERG implemented changes only at the base-case; no scenario/sensitivity analysis was re-run.

7.3.1. Full trial sample analysis: people who have received at least one prior therapy

The errors identified by the ERG that could potentially lead to alterations at the base-case in the analysis for the full trial population i.e. people who have received at least one prior therapy model results are:

- **Cost of monitoring – intravenous administration:** The cost of intravenous administration was double counted in both models. Though this double counting was removed for the subgroup analysis, the error was not corrected for the full trial population. The cost of monitoring was set at £186.
- **The cost of adverse event:** The cost of AE for Lymphopenia should be set at zero as it has no direct clinical relevance since infections are being treated as and when they arise. Removing the cost of Lymphopenia would decrease the cost of AEs for PANO/BTZ/DEX to £115 and to £62 for BTZ/DEX treatment groups.
- **Cost of monitoring – specialist visit:** The specialist visits should be conducted every 2 or 3 cycles. However, as noted above, in the model the specialist visits were applied per cycle. The frequency of activities for the disease monitoring was mismatched with the model inputs. These were corrected by the ERG in the model. The ERG applied the frequency of specialist visits of 0.5 i.e. every 2nd cycle.
-

7.3.2. Subgroup analysis: people who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen

Following the clarification stage, Novartis have provided some updated figures for the subgroup analysis. The frequency of the intravenous administration and the dose intensity were changed. These changes have reduced the cost of the treatment monitoring from £341.56 for the PANO/BTZ/DEX triplet to £185.56 when on treatment. The cost of the off treatment stage was correct in the initial submission (£92.78).

As explained above, the ERG have implemented the following changes to the model:

- the cost of the Lymphopenia to zero; and
- the frequency of the specialist visit has been set at 0.5 i.e. every 2nd cycle instead of per cycle.

7.3.3. Scenario analysis

We explored the impact on the ICER of the full population analysis if patients do not require to discontinue BTZ therapy despite having less than minimal response at cycle 4, as per PANORAMA-1 trial, in order to reflect the efficacy data used in the control arm of the model. This scenario was only explored for the full trial population which compared PANO/BTZ/DEX to BTZ/DEX since the stopping rule only applies to the BTZ/DEX treatment.

We also explored the impact on the ICER of the subgroup analysis of using different methodologies for indirect treatment comparisons in order to estimate the relative effectiveness between PANO/BTZ/DEX and LEN/DEX treatments.

7.4. Corrected base case outputs

7.4.1. People who have received at least one prior therapy

With the changes explained in the previous sections, Novartis' base case outputs are amended as reported in the tables below:

7.4.1.1. Cost of monitoring – intravenous administration

As already explained in Section **Error! Reference source not found.**, the cost of IV administration was double counted. The ERG replicate the cost-effectiveness analysis results here with the correct monitoring cost of £186 instead of £342 as in the original model. As shown below, there was a 1.21% increase in the ICER value from £79,025 to £78,071.

Table 74: Updated incremental cost-effectiveness analysis result with corrected monitoring cost

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
PANO/BTZ/DEX	£196,570	3.570	2.404	£43,950	0.773	0.563	£78,071
BTZ/DEX	£152,619	2.797	1.841				

Source: Corrected by the ERG

7.4.1.2. Cost of AE – Lymphopenia

Setting the cost of Lymphopenia at zero would decrease the total cost of Aes from £117 to £115 and from £63 to £62 for the PANO/BTZ/DEX and BTZ/DEX treatment groups, respectively. This change affects only slightly the ICER calculation from £79,025 to £79,002.

Table 75: Base-case ICER if the cost of Lymphopenia fixed at zero

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs. baseline (QALYs)
PANO/BTZ/DEX	£197,901	3.570	2.404	£44,474	0.773	0.563	£79,002
BTZ/DEX	£153,427	2.797	1.841				

Source: Corrected by the ERG

7.4.1.3. Cost of monitoring – specialist visit cost

Novartis applied per cycle specialist visit cost to the monitoring cost calculations. However, the ERG clinical expert stated that these visits were conducted every 2 or 3 cycles. The ERG re-run the model with the updated figure of specialist visit and changed the frequency of this activity from 1.00 to 0.50. The change of the figure by 0.50, changed the cost of the treatment monitoring from £341.56 to £263.56 while on treatment and cost of the monitoring from £92.78 to £53.78 while off treatment. There was a 1.36% decrease in the ICER value from £79,025 to £77,948.

Table 76: Base-case ICER with updated frequency of the specialist visit

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs))
PANO/BTZ/DEX	£196,770	3.570	2.404	£43,881	0.773	0.563	£77,948
BTZ/DEX	£152,889	2.797	1.841				

Source: Corrected by the ERG

7.4.1.4. Base case: all changes

In the next table, the ERG present the results of the modelling outcomes with all the following changes:

- Cost of monitoring set at £186; and
- Lymphopenia set at a zero instead of £167; and
- Specialist visit frequency every 2nd cycle instead of every cycle.

Table 77: Updated incremental cost-effectiveness analysis result with corrected monitoring cost, frequency of specialist visits, and cost of Lymphopenia set at zero

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
PANO/BTZ/DEX	£195,398	3.570	2.404	£43,330	0.773	0.563	£76,970
BTZ/DEX	£152,067	2.797	1.841				

Source: Corrected by the ERG

There was a 1.36% decrease in the ICER value from £79,025 to £76,970. This is the preferred ICER for the ERG.

When all these changes are incorporated, the probabilities of PANO/BTZ/DEX being cost-effective at WTP thresholds of £20,000, £30,000, £50,000 and £100,000 are 0%, 0%, 0% and 99%, respectively.

7.4.1.5. ERG scenario analysis: Implementation of the stopping rule

The ERG re-run the model without the stopping rule at cycle 4 together with the correct monitoring cost of £186. We found that this amendment would increase the ICER of 27% £78,071 to £99,318.

Table 78: Base-case ICER if not stopping rule at cycle 4

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
PANO/BTZ/DEX	£196,570	3.570	2.404	£48,863	0.702	0.495	£98,665
BTZ/DEX	£147,706	2.868	1.908				

Source: Corrected by the ERG

It is worth noting that BTZ modelled outcomes were not compared, for internal validation, against the corresponding observed outcomes in the clinical trial data source for the model because the model includes assumptions on the treatment pathway to replicate the UK clinical practice and BTZ label (i.e. stopping rules at cycle 4 and cycle 8).

7.4.2. People who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen

With the changes explained in the previous sections, Novartis' base case outputs are amended as reported in the tables below.

7.4.2.1. Cost of AE – Lymphopenia

Setting the cost of Lymphopenia at zero would decrease the total cost of Aes from £136.85 to £134.44 for the PANO/BTZ/DEX treatment group. The amended ICER calculations are presented below.

Table 79: Base-case ICER with zero cost of Lymphopenia – intravenous BTZ administration

Methodology	*Technologies*	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£) versus LEN/DEX*	*Incremental LYG versus LEN/DEX*	*Incremental QALYs versus LEN/DEX*	*ICER (£) Cost per Lys gained*[a]	*ICER (£) Cost per QALYs gained*[a]
'MAIC' deriving HRs from full trial populations	*PANO/BTZ/DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*0.071*	*0.029*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£148,567*	*2.216*	*1.491*					
'Unadjusted Cox' deriving HRs from subpopulation (2 to 3 prior lines)	*PANO/BTZ/DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*0.102*	*0.0518*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£147,632*	*2.186*	*1.469*					

Source: Corrected by the ERG

Table 80: Base-case ICER with zero cost of Lymphopenia – subcutaneous BTZ administration

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
'MAIC' deriving HRs from full trial populations	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.071	0.0295	£[redacted]	£[redacted]
	LEN/DEX	£148,567	2.216	1.491					
'Unadjusted Cox' deriving HRs from subpopulation (2 to 3 prior lines)	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.102	0.0518	£[redacted]	£[redacted]
	LEN/DEX	£147,632	2.186	1.469					

Source: Corrected by the ERG

7.4.2.2. Cost of monitoring – specialist visit cost

Changing the frequency of the specialist visit from 1 to 0.5 would affect the results. These results are presented below.

Table 81: Base-case ICER with updated specialist visit frequency – intravenous BTZ administration

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
'MAIC' deriving HRs from full trial populations	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.071	0.0295	£[redacted]	£[redacted]
	LEN/DEX	£148,524	2.216	1.491					
'Unadjusted Cox' deriving HRs from subpopulation (2 to 3 prior lines)	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.102	0.0518	£[redacted]	£[redacted]
	LEN/DEX	£147,591	2.186	1.469					

Source: Corrected by the ERG

Table 82: Base-case ICER with updated specialist visit frequency – subcutaneous BTZ administration

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
'MAIC' deriving HRs	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.071	0.0295	£[redacted]	£[redacted]

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
from full trial populations	LEN/DEX	£148,524	2.216	1.491					
'Unadjusted Cox' deriving HRs from subpopulation (2 to 3 prior lines)	PANO/BTZ/ DEX	£[redacted]	2.288	1.521	£[redacted]	0.102	0.0518	£[redacted]	£[redacted]
	LEN/DEX	£147,591	2.186	1.469					

Source: Corrected by the ERG

7.4.2.3. Base case: all changes

In the next table, the ERG present the results of the modelling outcomes with all the following changes:

- Lymphopenia set at a zero instead of £167; and
- Specialist visit frequency every 2nd cycle instead of every cycle.

Table 83: Base-case ICER with updated specialist visit frequency and zero cost of Lymphopenia – intravenous BTZ administration

Source: Produced by the ERG

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
'MAIC' deriving HRs from full trial populations	PANO/BTZ/ DEX	£[redacted]	2.288	1.521	£[redacted]	0.071	0.0295	£[redacted]	£[redacted]
	LEN/DEX	£148,524	2.216	1.491					
'Unadjusted Cox' deriving HRs from subpopulation (2 to 3 prior lines)	PANO/BTZ/ DEX	£[redacted]	2.288	1.521	£[redacted]	0.102	0.0518	£[redacted]	[redacted]
	LEN/DEX	£147,591	2.186	1.469					

Source: Corrected by the ERG

Table 84: Base-case ICER with updated specialist visit frequency and zero cost of Lymphopenia – subcutaneous BTZ administration

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
'MAIC' deriving HRs	PANO/BTZ/ DEX	£[redacted]	2.288	1.521	£[redacted]	0.071	0.0295	£[redacted]	£[redacted]

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
from full trial populations	*LEN/DEX*	*£148,524*	*2.216*	*1.491*					
'Unadjusted Cox' deriving HRs from subpopulation (2 to 3 prior lines)	*PANO/BTZ/ DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*0.102*	*0.0518*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£[redacted]*	*2.186*	*1.469*					

Source: Corrected by the ERG

7.4.2.4. ERG scenario analysis (no other changes)

Hazard ratios estimated using MTC method

The ERG re-run the model using the MTC method to estimate the HRs for PFS and OS for the full trial population.

We found that this amendment would decrease the ICER of 75% from £[redacted] to £[redacted] for intravenous BTZ administration and of 65% from £[redacted] to £[redacted] for subcutaneous BTZ administration.

The option of using the MTC method was not available to estimate the HRs of the subgroup of patients with 2 to 3 prior lines of therapy.

Table 85: Base-case ICER if HRs estimated using the MTC method – intravenous BTZ administration

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
'MTC' deriving HRs from full trial populations	*PANO/BTZ/ DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*0.269*	*0.1826*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£144,822*	*2.018*	*1.338*					

Source: Produced by the ERG

Table 86: Base-case ICER if HRs estimated using the MTC method – subcutaneous BTZ administration

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
'MTC' deriving HRs from full trial populations	*PANO/BTZ/ DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*0.269*	*0.1826*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£144,822*	*2.018*	*1.338*					

Hazard ratios estimated using Naïve comparison method

The ERG re-run the model using the Naïve comparison method to estimate the HRs for PFS and OS for the full trial population and the subgroup of patients with 2 to 3 prior lines of therapy.

Table 87: Base-case ICER if HRs estimated using the Naïve comparison method – intravenous BTZ administration

Methodology	*Technologies*	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£) versus LEN/DEX*	*Incremental LYG versus LEN/DEX*	*Incremental QALYs versus LEN/DEX*	*ICER (£) Cost per Lys gained[a]*	*ICER (£) Cost per QALYs gained[a]*
'Naïve comparison' deriving HRs from full trial populations	*PANO/BTZ/DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*0.009*	*-0.0066*	*£[redacted]*	*[redacted]*
	LEN/DEX	*£155,466*	*2.279*	*1.527*					
''Naïve comparison' deriving HRs from subpopulation (2 to 3 prior lines)	*PANO/BTZ/DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*-0.061*	*-0.0465*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£163,203*	*2.348*	*1.567*					

Source: Produced by the ERG

Table 88: Base-case ICER if HRs estimated using the Naïve comparison method – subcutaneous BTZ administration

Methodology	*Technologies*	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£) versus LEN/DEX*	*Incremental LYG versus LEN/DEX*	*Incremental QALYs versus LEN/DEX*	*ICER (£) Cost per Lys gained[a]*	*ICER (£) Cost per QALYs gained[a]*
'MAIC' deriving HRs from full trial populations	*PANO/BTZ/DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*0.071*	*0.0295*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£148,524*	*2.216*	*1.491*					
'Unadjusted Cox' deriving HRs from subpopulation (2 to 3 prior lines)	*PANO/BTZ/DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*-0.061*	*-0.0465*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£163,203*	*2.348*	*1.567*					

Source: Produced by the ERG

Hazard ratios estimated using the Unadjusted Cox method

The ERG re-run the model using the Unadjusted Cox method to estimate the HRs for PFS and OS for the full trial population only since this method was used for the subgroup of patients with 2 to 3 prior lines of therapy in the base case.

Table 89: Base-case ICER if HRs estimated using the Unadjusted Cox method – intravenous BTZ administration

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
'Unadjusted Cox' deriving HRs from full trial populations	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	-0.004	-0.0230	[redacted]	[redacted]
	LEN/DEX	£152,456	2.292	1.544					

Source: Produced by the ERG

Table 90: Base-case ICER if HRs estimated using the Unadjusted Cox method – subcutaneous BTZ administration

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
'MAIC' deriving HRs from full trial populations	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	-0.004	-0.023	£[redacted]	£[redacted]
	LEN/DEX	£152,456	2.292	1.544					

Source: Produced by the ERG

Hazard ratios estimated using the MAIC method

The ERG re-run the model using the MAIC method to estimate the HRs for PFS and OS for the group of patients with 2 to 3 prior lines of therapy only since this method was used for the full trial population in the base case.

We found that this amendment would decrease the ICER of 18% from £[redacted] to £[redacted] for intravenous BTZ administration and increase the ICER of 38% from £[redacted] to £[redacted] for subcutaneous BTZ administration.

Table 91: Base-case ICER if HRs estimated using the MAIC method – intravenous BTZ administration

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
'MAIC' deriving HRs from subpopulation (2 to 3 prior lines)	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.461	0.2839	£[redacted]	£[redacted]
	LEN/DEX	£120,148	1.827	1.237					

Source: Produced by the ERG

Table 92: Base-case ICER if HRs estimated using the MAIC method – subcutaneous BTZ administration

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
MAIC' deriving HRs from subpopulation (2 to 3 prior lines)	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.2839	0.461	£[redacted]	£[redacted]
	LEN/DEX	£120,148	1.827	1.237					

Source: Produced by the ERG

The ERG believe that this indirect comparison may be the preferred option to estimate the relative effectiveness between LEN/DEX and PANO/BTZ/DEX. The generated ICER for the subcutaneous administration of BTZ is £[redacted]. However, as explained in more details in Section **Error! Reference source not found.** the MAIC estimates are likely to be unreliable and biased by unobserved confounding.

In addition the ERG re-run the model using the MAIC method with the cost of Lymphopenia set at a zero instead of £167; and the specialist visit frequency at every 2nd cycle instead of every cycle, the

Table 93: Base-case ICER if HRs estimated using the MAIC method with updated specialist visit frequency and zero cost of Lymphopenia – subcutaneous BTZ administration

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
MAIC' deriving HRs from subpopulation (2 to 3 prior lines)	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.2839	0.461	£[redacted]	£[redacted]
	LEN/DEX	£120,108	1.827	1.237					

Source: Produced by the ERG

The ERG believe that the generated ICER for the subcutaneous administration of BTZ of £[redacted] is the most plausible ICER for patients with 2 to 3 prior lines of therapy.

8. Summary of clinical and cost-effectiveness issues

Novartis have reported analyses examining the cost-effectiveness of:

- PANO/BTZ/DEX compared with BTZ/DEX in multiple myeloma patients who have received at least one prior therapy (full trial population);
- PANO/BTZ/DEX compared with LEN/DEX in multiple myeloma patients who have received two or three prior lines of therapy including an IMiD and BTZ (subgroup analysis).

The two cost-effectiveness analyses have been reported for the full trial sample for people who have received at least one prior therapy and for the subgroup of people who have had received two or three prior lines of therapy including an IMiD and BTZ.

8.1. Full trial sample analysis: people who have received at least one prior therapy

- The base case cost-effectiveness analysis gives an ICER of £79,025 per QALY gained for PANO/BTZ/DEX relative to BTZ/DEX (incremental cost of £44,487 and incremental health gain of 0.563 QALYs). After correction of the double counting of the cost of IV administration, the ICER decreases to £78,071 per QALY gained.

- A statistically significant increase in median PFS has been reported for PANO/BTZ/DEX relative to BTZ/DEX in the PANORAMA-1 trial. Median OS data (albeit immature) show an improvement with PANO/BTZ/DEX but not a statistically significant difference.

- The model relied almost exclusively on PANORAMA-1 for effectiveness data despite aspects of the trial being inconsistent with UK clinical practice: the absence of a stopping rule at cycle 4 in PANORAMA-1 to test for response with BTZ and BTZ/DEX treatment being given beyond cycle 8.

- After considering design features of the model which attempted to allow for differences between PANORAMA-1 and UK clinical practice, concerns remained around the modelled estimates of OS compared with the Kaplan-Meier curves from PANORAMA-1.

- The divergence between the modelled survival functions and the Kaplan-Meier estimates, with the modelled estimates exceeding the observed survival data in the PANO/BTZ/DEX group but being lower than the observed data in the BTZ/DEX group suggests that the modelled survival estimates may have exaggerated the benefits of PANO/BTZ/DEX.

- Whereas the analysis includes costs associated with individual AEs, the utility calculations do not make an adjustment for utility decrements associated with AEs; neither was a search conducted for evidence on AEs which might not be identified within the trial setting.

- Higher average utilities for the PANO/BTZ/DEX group, mapped from quality of life data collected as part of the trial, raise questions around the ability of the quality of life assessments to capture the impact of adverse events, given the emphasis placed on the poorer safety profile associated with the PANO/BTZ/DEX arm of PANORAMA-1. The QALY gains associated with PANO/BTZ/DEX may therefore have been overestimated.

- The results of the one-way sensitivity analysis are difficult to interpret and the variables investigated do not include patient age despite a difference between the age of patients enrolled into PANORAMA-1 and those entering cycle 1 of the model.

- Given that the results of the model are relatively invariant to changes in time horizon, and given the concerns about the modelled survival estimates, a scenario analysis based on observed within-trial data would have been useful.

For the ERG, the most plausible ICER for the full trial population analysis of people who have received at least one prior therapy accounts for the correction of the monitoring cost, the frequency of specialist visits, and the cost of Lymphopenia. This ICER is £76,970 per QALY gained for PANO/BTZ/DEX vs. BTZ/DEX

8.2. Subgroup analysis: people who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen

Drawing on the PANORAMA-1 study and an indirect treatment comparison using data from the pooled data from MM-009 and MM-010 trials, Novartis have estimated the cost-effectiveness of PANO/BTZ/DEX compared with LEN/DEX in multiple myeloma patients who have received at least 2 prior lines of therapy including an IMiD and BTZ.

- While LEN/DEX is a relevant comparator for PANO/BTZ/DEX in patients who have received at least two prior lines of therapy including an IMiD and BTZ, the subgroup analysis does not explain why BTZ/DEX is not considered as a comparator in this subgroup. Thus, the company have missed the opportunity to compare the cost-effectiveness of PANO/BTZ/DEX and BTZ/DEX in this subgroup. Additionally, from a cost-effectiveness perspective, if BTZ/DEX was omitted from this analysis, it may be questioned whether these patients should have been excluded from the main cost-effectiveness analysis. The interpretation of the cost-effectiveness results should take account of the absence of BTZ/DEX as a comparator in the subgroup analysis of patients who have received at least 2 prior lines of therapy including an IMiD and BTZ.

- The indirect treatment comparison method by which the hazard ratios for progression free survival and overall survival between LEN/DEX and PANO/BTZ/DEX was estimated lacks robustness. Indeed, the Unadjusted Cox regression used to estimate the hazard ratios for the subgroups who received 2 to 3 prior lines of therapy from the PANORAMA-1 trial generated Kaplan-Meier curves for the two arms which were not parallel. Therefore this method is not valid in this application as the Kaplan-Meier curves do not satisfy the key assumption of proportional hazards.

- The efficacy data (i.e. HRs for LEN/DEX vs. PANO) is coming from the subpopulation of patients who have received 2 to 3 prior line of treatment which is wider than the population of the subgroup analysis which considered people patients who received two or three prior lines of therapy including an **IMiD and BTZ.** It is unclear therefore whether the effectiveness data included in the subgroup analysis are appropriate for the patient group of interest.

- The small difference in QALYs between the two therapies suggests that it is difficult to distinguish the efficacy between PANO/BTZ/DEX and LEN/DEX in this subpopulation and makes the results difficult to interpret.

For the ERG, the most plausible ICER for the subgroup of at least 2 prior lines of therapy including an IMiD and BTZ is when the MAIC method is used to estimate the HRs for PFS and OS for and accounts for the correction of the frequency of specialist visits and the cost of Lymphopenia with BTZ administered subcutaneously. This ICER is £[redacted] per QALY gained for PANO/BTZ/DEX vs. LEN/DEX.

9. References

Acaster S, Gaugris S, Velikova G, Yong K, Lloyd AJ. Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: a UK cross-sectional survey. Support Care Cancer 2013;21:599–607.

Ara, R., Wailoo, A.J. NICE DSU Technical Support Document 12: The use of health state utility values in decision models. 2011. Available from http://www.nicedsu.org.uk.

Bird JM, Owen RG, D'Sa S et al. Guidelines for the diagnosis and management of multiple myeloma 2014. Available from: http://www.bcshguidelines.com/documents/MYELOMA_GUIDELINE_Feb_2014_for_BCSH.pdf. (Accessed 4 June 2014).

Brown RE, Stern S, Dhanasiri S, Schey S. Lenalidomide for multiple myeloma: cost-effectiveness in patients with one prior therapy in England and Wales. Eur J Health Econ 2013;14 507–14.

Cancer Research UK. Myeloma survival statistics. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/survival#heading-Zero. (Accessed 9 July 2015).

Cancer Research UK. Myeloma survival statistics. Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/myeloma/survival/. (Accessed 17 June 2014).

Celgene. NICE Single Technology Appraisal (STA) - Pomalidomide for relapsed and refractory multiple myeloma. June 2014.

Celgene. RevlIMiD (lenalidomide) Summary of product characteristics. Available from: https://www.medicines.org.uk/emc/medicine/19841. (Accessed 8 May 2015).

Dimopoulos M, Spencer A, Attal M et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007;357 2123–32.

Dimopoulos MA, Chen C, Spencer A et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia 2009;23:2147–52.

Dimopoulos MA, Orlowski RZ, Facon T et al. Retrospective matched-pair analysis of the efficacy and safety Of bortezomib plus dexamethasone versus bortezomib monotherapy in patients (Pts) with relapsed multiple myeloma (MM). Poster presented at the 55th ASH Annual Meeting and Exposition, 7–10 December 2013, New Orleans, Louisiana, USA.

Durie BG, Harousseau JL, Miguel JS et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467–73.

Drummond, MF. Jefferson, TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party, British Medical Journal, 313(7052): 275–83. 1996.

EMA. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003725/smops/Positive/human_smop_000846.jsp&mid=WC0b01ac058001d127. (Accessed 30/06/15).

European Haematology Association. Available from: http://learningcenter.ehaweb.org/eha/2015/20th/100518/philippe.moreau.analysis.of.outcomes.by.response.for.patients.with.relapsed.or.html?f=l5550p16m3.

Food & Drug Administration. FDA Briefing Document Oncologic Drugs Advisory Committee Meeting, 6 November 2014.NDA 205353 panobinostat (Farydak) Novartis. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM421623.pdf. (Accessed 30 January 2015).

Fragoulakis V, Kastritis E, Psaltopoulou T, Maniadakis N. Economic evaluation of therapies for patients suffering from relapsed-refractory multiple myeloma in Greece. Cancer Manag Res 2013;5 37–48.

Garderet L, Iacobelli S, Moreau P et al. Superiority of the triple combination of bortezomib-thalidomide-dexamethasone over the dual combination of thalidomide-dexamethasone in patients with multiple myeloma progressing or relapsing after autologous transplantation: the MMVAR/IFM 2005-04 Randomized Phase III Trial from the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2012;30:2475–82

Gooding S, Lau I-J, Sheikh M et al. Double refractory myeloma: analysis of clinical outcomes and medical-resource utilisation in a single centre Blood 2013;122:Abstract 1727.

Green C, Bryant J, Takeda A et al. Bortezomib for the treatment of multiple myeloma patients. Health Technol Assess 2009;13 (Suppl 1):29–33.

Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9.

lade J, Samson D, Reece D et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol 1998;102:1115–23.

Haematological Malignancy Research Network. Clinical management and outcome of myeloma. Version 3.0.

Hjorth M, Hjertner O, Knudsen LM et al. Thalidomide and dexamethasone vs. bortezomib and dexamethasone for melphalan refractory myeloma: a randomized study. Eur J Haematol 2012;88 485–96.

Hornberger J, Rickert J, Dhawan R et al. The cost-effectiveness of bortezomib in relapsed/refractory multiple myeloma: Swedish perspective. Eur J Haematol 2010;85 484–91.

Jiang Y, Spencer M, Gauthier A, Pacou M. A cost-effectiveness analysis for second-line treatment of relapsed/refractory (RR) multiple myeloma (MM) in the United Kingdom. Value Health 2011;14:A452.

Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching (2014).

Latimer, N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011.

Moller J, Nicklasson L, Murthy A. Cost-effectiveness of novel relapsed-refractory multiple myeloma therapies in Norway: lenalidomide plus dexamethasone vs bortezomib. J Med Econ 2011;14 690–7.
National Chemotherapy Algorithms. Multiple myeloma. Available from: https://www.engage.england.nhs.uk/consultation/specialised-services-consultation/user_uploads/chemothrpy-algrthms-mltpl-myeloma.pdf. (Accessed 8 May 2015).

National Audit Office. End of life care. 2008. Available at: http://www.nao.org.uk/wp-content/uploads/2008/11/07081043.pdf (Accessed: 14 January 2014)

National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Available from: http://www.nice.org.uk/article/pmg9/chapter/Foreword. (Accessed 12 March 2015).

National Institute for Health and Care Excellence. Technology Appraisal 311: Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation. April 2014. Available from: https://www.nice.org.uk/guidance/ta311. (Accessed 5 June 2014).

National Institute for Health and Care Excellence. Technology Appraisal 228: Bortezomib and thalidomide for the first-line treatment of multiple myeloma. July 2011. Available from: https://www.nice.org.uk/guidance/ta228. (Accessed 5 June 2014).

National Institute for Health and Care Excellence. Technology Appraisal 129: Bortezomib monotherapy for relapsed multiple myeloma. October 2007. Available from: www.nice.org.uk/TA129. (Accessed 4 October 2013).

National Institute for Health and Care Excellence. Technology Appraisal 171: Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. June 2009. Available from: http://www.nice.org.uk/TA171. (Accessed 4 October 2013).

National Institute for Health and Care Excellence. Technology Appraisal 338. Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib. 2015. Available from: https://www.nice.org.uk/guidance/ta338

National Institute for Health and Care Excellence. Critical appraisal checklist. 2008

National Institute for Health and Care Excellence. 2014. Relevance to NICE guidance programmes. Available from https://www.nice.org.uk/advice/esnm32/chapter/Relevance-to-NICE-guidance-programmes (Acessed 24/07/2015).

NICE. Head injury: triage, assessment, investigation and early management of head injury in children, young people and adults.2014. Available from: http://www.nice.org.uk/guidance/cg176/resources/cg176-head-injury-costing-template2

Orlowski RZ, Nagler A, Sonneveld P et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. J Clin Oncol 2007;25:3892–901.

Rajkumar SV, Harousseau JL, Durie B et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Blood 2015:117;15:4691-5.

Richardson PG, Barlogie B, Berenson J et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003;348:2609–17.

Richardson PG, Schlossman RL, Alsina M et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. Blood 2013;122:2331–7.

Richardson PG, Sonneveld P, Schuster MW et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005;352:2487–98.

San Miguel J, Weisel K, Moreau P et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. The lancet oncology 2013;14:1055–66.

San-Miguel J, Hungria VTM, Yoon S-S et al. Efficacy and safety based on duration of treatment of panobinostat plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma in the phase 3 Panorama 1 study. Blood 2014;124:4742.

San-Miguel JF, Hungria VT, Yoon SS et al. Correction to Lancet Oncol 2014; 15: 1195–206. Lancet Oncol 2015;16:e6.

San-Miguel JF, Hungria VT, Yoon SS et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15:1195–206.

San-Miguel JF, Richardson PG, Gunther A et al. Phase Ib study of panobinostat and bortezomib in relapsed or relapsed and refractory multiple myeloma. J Clin Oncol 2013;31:3696–703.

Schey S, Stern S, Dhanasiri S, Brown R. Cost-effectiveness if lenalidomide/dexamethasone in multiple-myeloma patients with prior thalidomide therapy. Haematologica 2012;97 (Suppl 1):1087.

Siegel D, Richardson D, Dimopoulos K, al e. Efficacy and safety of pomalidomide plus low-dose dexamethasone in advanced multiple myeloma: results of randomized phase 2 and 3 trials (MM-002/MM-003) Abstract presented at American Society of Hematology annual meeting, New Orleans, LA , USA, 7-10 December 2013; Abstract 3185. Available from: http://www.bloodjournal.org/content/122/21/3185?sso-checked=true.

Signorovitch JE, Wu EQ, Yu AP et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. Pharmacoeconomics 2010;28:935–45.

Stadtmauer EA, Weber DM, Niesvizky R et al. Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma. Eur J Haematol 2009;82:426–32.

Walker SA, Izmirlieva MA, Mehta P. A cross-country comparison of second-line multiple myeloma treatments. Value Health 2011;14:A175

Weber DM, Chen C, Niesvizky R et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357 2133–4

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Panobinostat for treating multiple myeloma in people who have received at least one prior therapy [ID663]

You are asked to check the ERG report from PenTAG to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **9am, Wednesday 5 August** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Inaccuracy

	Description of problem	Description of proposed amendment	Justification for amendment	ERG response
1	ERG states that only the MAIC method was adjusted for baseline differences. Section 1.2, page 13; section 4.4, page 92	N/A	The MAIC is not the only adjusted method. In fact, the "Unadjusted Cox" method, when applied on the subset of patients with 2-3 prior lines of treatment, was adjusted for the number of prior lines as well as by the exclusion of patients who had received prior lenalidomide. In retrospect, we realise it would have been less confusing had we called it "partially adjusted".	The company's response is contradictory with their own choice of labels (i.e. they refer to the analysis in question as 'Unadjusted Cox' and now they have called it the partially adjusted Cox). This new proposed use of terms is also at odds with standard semantic practice in biostatistics; unadjusted is used to refer to the fact that the analysis did not control for differences in baseline characteristics that may potentially affect outcome, other than treatment status (confounding). The ERG's point is precisely that no such adjustment was made in the statistical analysis of the included sample and that confounding is likely to be present in the estimated treatment effect. However the text has been amended for clarity. P 15 change made: "which, **compared with the other methods, made a more comprehensive adjustmen**t for baseline differences across treatment groups". P 92 change made: "**Analyses unadjusted or partially adjusted** for baseline differences are likely to be biased (including the analyses using individual patient data, which also invalidly assume proportional hazards) **and those based on the MAIC method** suffer from low statistical power (as evidenced by the effective sample sizes)."

2	"(...) the utility calculations do not make an adjustment for utility decrements associated with AEs (...)" - Section 1.5.1, Page 17	N/A	Utility values are mapped directly from HRQoL data collected in the trial setting. The mapped data represent the utility value associated to the specific health sates adequately including the effects of the treatment. Hence the utility value of 0.679 (pre-progression on PAN/BTZ/DEX treatment) as compared with 0.716 (pre-progression on LEN/DEX treatment in comparison per the licensed indication.	No issue of factual accuracy identified. Additionally, HRQL outcomes (from EORTC, QLQ30 and EORTC QLQ-MY20) were measured at specific follow-up points (at screening, before study drug treatment on cycle 1 day 1 and every six weeks thereafter) and so are unlikely to adequately capture the impact on QoL of treatment-related acute adverse events.
3	"The indirect treatment comparison method by which the hazard ratios for progression free survival and overall survival between LEN/DEX and PANO/BTZ/DEX was estimated lacks robustness." - Section 1.5.2; page 17	N/A	Novartis believes that the robustness came from the fact that all possible methodologies were modelled, with the results reproducible from the model submitted.	No issue of factual accuracy identified.
4	"Therefore this (Unadjusted Cox based on subpopulation data) method is not valid in this application as the Kaplan-Meier curves do not satisfy the key assumption of proportional hazards." Section 1.5.2; page	N/A	When testing the proportional hazard assumption based on Schoenfeld residuals, the following results were acquired: • Unadjusted Cox method applied on the population with 2-3 prior lines of treatment with 95% CI and a p-value (Schoenfeld residuals); PFS and OS **PFS** | **OS**	No issue of factual accuracy identified. The 95% CIs and p-value for the hazard rations were not originally provided by the company in the submission. The large p-value (0.98) for the HR OS using the Unadjusted Cox method (applied on the patient pool with 2-3 prior lines) means that there is no evidence to reject the hypothesis that the residuals are

<table>
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<td>17; section 4.4, page 92</td>
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<tr><td></td><td>HR</td><td>95% CI</td><td>HR</td><td>95% CI</td></tr>
<tr><td>Unadjusted Cox</td><td>1.061</td><td>0.80 – 1.41</td><td>1.075</td><td>0.76 – 1.53</td></tr>
<tr><td>p-value (Schoenfeld residuals)</td><td colspan="2">0.04</td><td colspan="2">0.98</td></tr>
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MAIC method applied on the population with 2-3 prior lines of treatment with 95% CI and a p-value (Schoenfeld residuals); PFS and OS
<table>
<tr><td></td><td colspan="2">PFS</td><td colspan="2">OS</td></tr>
<tr><td></td><td>HR</td><td>95% CI</td><td>HR</td><td>95% CI</td></tr>
<tr><td>Matching adjusted Cox</td><td>1.108</td><td>0.58 – 2.12</td><td>1.413</td><td>0.62 – 3.24</td></tr>
<tr><td>p-value (Schoenfeld residuals)</td><td colspan="2">0.01</td><td colspan="2">< 0.01</td></tr>
</table>
Therefore, the PH assumption was met for OS using the Unadjusted Cox method (applied on the patient pool with 2-3 prior lines).
Data also shows that PH assumption is not met for MAIC method (applied on the patient pool with 2-3 prior lines).
</td>
<td>uncorrelated with time and therefore the Proportional hazard assumption (PH) could be used.

However, it is clear graphically that the curves are crossing and that the shape of the survival curves are unlikely to be the same across the two arms, which is highly suggestive that the PH assumption is invalid in this application (Latimer 2011). In this case, choosing to use the PH model on the basis of the result of the Schoenfeld residual test alone may be invalid as the test does not account for nonlinear relationship between the Schoenfeld residuals and time (Thereneau and Gramsch 2000). The company should have provided a plot of the Schoenfeld residuals against time to support the results of the tests.
The company should have also provided a Log-cumulative hazard plots in order to determine the suitability of the PH assumption. As described in the DSU paper (Latimer 2011) 'if the plots for the two treatment groups are parallel, proportional hazards models should be considered and assessed further, whereas if they are not parallel, individual model fitting for each treatment arm should be undertaken using a suitable model and assessed further.'

The ERG think that had the company presented these additional diagnostic checks they would have found further graphical information invalidating the specification test based on Schoehfled residuals and the PH model itself.</td>
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<td>5</td>
<td>"Following LEN therapy, BTZ can be used in the 3rd line." -</td>
<td>N/A</td>
<td>Since NICE has never approved BTZ based regimen beyond 2nd line and NCDF delisted bortezomib in combination with dexamethasone for patients who have</td>
<td>P 25 change made for clarity:

“According to the reimbursement algorithm, if a</td>
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	Section 2.2; page 25; section 3.3, page 30; section 6.2.1, page 152		received prior bortezomib, BTZ can not be used in the 3rd line setting as ERG describes.	**patient has BTZ at induction, then either LEN (NCDF funded) or BTZ (TA129) can be used in the 2nd line. If BTZ is used as 2nd line, then the patient would receive LEN/DEX (TA171). The combination of PANO/BTZ/DEX can then be used instead (as 3rd line).** **According to our clinical expert, a medical decision could be made to use BTZ in 3rd line therapy after BTZ/DEX induction and LEN as 2nd line, which goes beyond the reimbursement decision. Then the combination of PANO/BTZ/DEX could be used instead as 3rd line**."
6	"(...) , the source of the presented number (eligible patient pool) is not presented and does not make any further reference to the cited number of 1300." - Section 3.1, page 27	N/A	Novartis explains the way of calculation of the eligible patient pool in section 3.3, albeit without doing the math in the text (Which however is done in section 6, assuming an eligible patient pool of 1348 in year 2015).	Novartis should have referred to the appropriate section for this calculation or could have presented the number in the brackets (1348). Novartis state that "*there are 3117 patients with MM in England and Wales, of whom 2194 will be receiving active treatment in first line setting of which 86.5% receives 2nd line treatment where the bortezomib treatment rate is approximately 71%."* This 71% results in 1348 of patients with BTZ use in second line following IMiD or SCT (section 6, pg. 216). P 27 the text has been amended: "The company also note that approximately 1300 patients in England and Wales would be eligible to receive PANO annually **– a title of the paragraph 2 on page 41. The figure is calculated from the HMRN data and equals to 1348 patients. The detailed calculation is only presented later on in Section 6 of the submission".**
7	"(...) the submitted	N/A	The last systematic review update was carried out on 9th	P 32 text removed:

	literature searches being over six months out of date." - Section 4.1.1, page 32		December 2014 with the results shared in the submission on the 20th May 2015. Thus the last SR update was 5.33 months out of date of the submission, therefore within the 6 months limit in line with the respective Guidance.	'Within the submission, the company observe the paucity of mature trial data and, we note, is aware of further data that is now available to them. In view of additional data **being available, the ERG asked** the company to update their literature searches. The company declined to do so.
8	"Novartis suggest that the MAIC method "provides the most appropriate approach for deriving the relative efficacies of the PANO/BTZ/DEX versus LEN/DEX for use in the economic evaluation"." - Section 4.3.3.4, page 89	N/A	This partial quote is taken out of context. In Section 1.7 of Appendix 17 we also suggest that the MAIC method may only work with bigger sample size. In case of the subpopulation with 2-3 prior lines of treatment the matching reduces the effective sample to 23 patients, which constitutes a high risk of bias and significantly underestimates the OS as compared to the reported survival in that subgroup (Stadtmauer 2009). Therefore, in the same section we suggest having two base case analyses: the MAIC conducted only on the full population set; and the unadjusted cox method conducted on the smaller sample with 2-3 prior lines of treatments.	No issue of factual accuracy identified. Additionally, the company do not present a figure for the amount of underestimation of OS. Stadtmauer report a median OS of 35.8 months for the population who have received at least two prior lines of therapy. No OS value is reported using either the Unadjusted Cox or MAIC method.
9	"The HRQL was not measured in PANORAMA-1 trial during TFI therefore it was necessary to assume that the HRQL in that state was equal to the last cycle of treatment." - section 4.4, page 91	"The HRQL was not measured in PANORAMA-1 trial during TFI therefore it was necessary to assume that the HRQL in that state was equal to that reported by Acaster et al."	This assumption was made only in the full trial population comparison. In the CE model for the restricted population, the utility value reported by Acaster et al* was applied. ***Reference**: Acaster S, Gaugris S, Velikova G, Yong K, Lloyd AJ. Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: a UK cross-sectional survey. *Support Care Cancer* 2013;21:599–607.	No issue of factual accuracy identified as the passage relate to the section 5.4.2 of the submission, however the text has been amended for clarity. P 91 change made: "The HRQL was not measured in the PANORAMA-1 trial during TFI therefore it was necessary to **extrapolate from the last cycle of treatment (full trial sample analysis) or use the utility reported in Acaster et al. (subgroup analysis).**"

10	Incorrect data in table 88, page 172; table 90, page 173; tables 92, 93, page 174;	N/A	Table shows results from a different method or switching up data in cells or naming the underlying method incorrectly.	Table 88 and 90 have been updated accordingly. Table 92 and 93 are correct.

Issue 2 Clarification

	Description of problem	Description of proposed amendment	Justification for amendment	ERG response
11	(...) subgroup analysis does not explain why BTZ/DEX is not considered as a comparator in this subgroup (...)" - Section 1.5.2; page 17	N/A	The lack of BTZ/DEX as a comparator is related to the current UK clinical guidelines and NICE recommendations which exclude the use of BTZ/DEX combination after prior BTZ based regimen. Since panobinostat's final licence requires prior bortezomib treatment explicitly, BTZ/DEX treatment was not considered as a valid comparator.	No issue of factual accuracy identified as this explanation was not provided in the original submission.
12	"The Unadjusted Cox method was chosen to estimate the relative effectiveness between those two treatments. For this reason , the ERG lack confidence in the final ICER presented." - Section 1.4.2, page 16	N/A	It suggests that the method chosen by the manufacturer is less adequate that the one chosen by the ERG. Novartis believes it is the opposite after assessing the various results in a broader context (PH assumptions for both PFS and OS, sample size, matching with clinical data, visual inspection of the curves and analysing the 95% CIs.	No issue of factual accuracy identified The ERG believe that the use of the Unadjusted Cox method which does not control for differences in baseline characteristics is very likely to add a greater bias than a method which does adjust for or differences between the trials in terms of patient and disease characteristics at baseline. For instance, there is a 9% decrease in serum ß2-microglobulin level (> 2.5 mg/L) between the MM-009 and MM-010 trial population n = not reported) and the PANORAMA-1 patient population who have received 2 to 3 prior lines of treatment (n = 142), both excluding patients who had previously received LEN (i.e. 74.5%

				vs. 67.6%, respectively). Additionally, as described above visual inspection of the survival curves suggest the PH assumption is invalid in this application and the Schoenfeld residual test alone may be invalid as the test does not account for nonlinear relationship between the Schoenfeld residuals and time. The company should have provided a plot of the Schoenfeld residuals against time to support the results of the tests.
13	"It is unclear therefore whether the effectiveness data included in the subgroup analysis are appropriate for the patient group of interest." - Section 1.5.2; page 18	N/A	It suggests that PFS and OS HRs could have been generated on the specific subgroup that is in question (i.e. at least 2 prior lines including an IMID and BTZ). Unfortunately, as explained in Appendix 17 of the manufacturer's submission, such data is not available on LEN/DEX. The closest proxy was the subgroup of patients with 2-3 prior lines of treatment reported by Stadtmauer in 2009. The data for the subgroup equivalent to that was also analysed from patient level data from the PANORAMA-1 trial. Novartis chose a proxy dataset available for LEN/DEX closest to the licensed subgroup at question.	No issue of factual accuracy identified
14	"For the ERG, the most plausible ICER is when the MAIC method (...)" - Section 1.6; page 18; section 7.4.2.4, page 174	N/A	Novartis is concerned that there has been no full justification presented in the ERG report to support this statement.	No issue of factual accuracy identified
15	"This, however, contradicts the company's claim based on BCSH guidance that many	N/A	Novartis's statements are based on the available retrospective analysis. Section 3.3 of the manufacturer's submission refers to an analysis of treatment outcomes for the HMRN cohort of 1543 patients which shows that only 18% of the patients receive ASCT, hence induction	No issue of factual accuracy identified. We are happy with the wording in the text since the ERG clinical expert comment was included. The comment refers to the BCSH guidance and not the

	UK patients receive THAL based therapy at induction". - Section 2.2, page 25.		treatment prior to that. So while it might as well be true that most who receive ASCT will receive BTZ based therapy as induction, only a minority (18%) of the patients will go through ASCT in this setting.	HMRN cohort.
16	Misinterpretation of the term rrMM in the submission dossier. Section 3.1, page 26, page 27; section 4.1, page 52; Section 4.3.2, page 73; section 4.4, page 91	N/A	rrMM stands for “relapsed and/or refractory”, i.e. 'relapsed' or 'relapsed and refractory' or refractory (primary)'.	No issue of factual accuracy identified. On page 27 the ERG have provided the clinical expert’s view and explained that “when clinicians talk of rrMM they typically mean relapsed, relapsed and refractory and primary refractory MM as defined in the paper published in Rajkumar et al”. This however, does not eliminate the confusion over the use of terms for the PANO indication.
17	"The ERG is not clear why the results for PFS are only reported for 381 patients instead of 387 for the treatment arm and 377 patients instead of 381 for the control arm." Section 4.2.1, page 52; section 4.2.2, page 56	N/A	Table 13 incorrectly states the number of patients analysed for PFS. The number 381 incorrectly refers to the safety set, while PFS analysis was conducted on the FAS, i.e. all the 387 patients randomized.	The numbers were incorrect on a number of occasions in the submission. The ERG added the following statement on page 52: The ERG **was** not clear why the results for PFS **were** only reported for 381 patients instead of 387 for the treatment arm and 377 patients instead of 381 for the control arm. **Following the Factual Error Check, Novartis clarified that PFS analysis was actually conducted for the FAS i.e. 387 and 377 for the treatment arm and control arm, respectively.** P56: Sentence has been deleted: **“Once again, the ERG is not clear why the results for PFS are only reported for 381 patients instead of 387 for the treatment arm and 377 patients instead of 381 for the control arm”**.
18	"There is some confusion on the value cited in Section 4.7.5 of the	N/A	Document was not updated before submission although, in the submitted model, the QALY difference is 0.56 (discounted) (0.38 for the TFI, 0.54 vs 0.16) in the base	No issue of factual accuracy identified.

	submission which states that “patients receiving panobinostat triplet therapy gain 0.53 quality-adjusted life year (QALY) over patients receiving BTZ/DEX.” Section 4.2.4, page 62		case analysis.	
19	"Novartis did not present any Kaplan-Meir curves for the naïve comparison." - Section 4.3.3.2, page	N/A	In the case of the naive comparison the median PFS and OS values were used to set up a HR for each. KM curves held no relevance in applying that method.	No issue of factual accuracy identified.
20	"Patients who received prior LEN based treatment in the PANORAMA-1 trial were excluded from the analysis. Novartis do not give any explanation to why this was done." - Section 4.3.3.3, page 82	N/A	This exercise was done to match the two patient cohorts by two of the most important criteria, i.e. the use of prior LEN/DEX and the number of prior lines of treatment.	No issue of factual accuracy identified.
21	"Therefore the hazard ratio estimate is likely to be an invalid, meaningless summary measure of the relative	N/A	While we agree that the proportional hazard assumption was not met using the Unadjusted Cox method, the same is true for the MAIC method. Further, there is uncertainty in the MAIC related to the “extreme weights” some patients received through the matching process which reduced the effective sample size to 23 patients (23%) (as	No issue of factual accuracy identified. As explained above and in the report, the ERG believe that although the MAIC method is likely to be unreliable and biased due to a low statistical power, it addresses some of the issues that the other methods do not consider i.e. adjustment for patient baseline

	effectiveness" - Section 4.3.3.3, page 84; section 4.3.3.5, page 90		also pointed out in the ERG report on page 90). In contrast, the Unadjusted Cox method keeps a relatively high sample size while still being adjusted in the two most relevant criteria, which are the use of prior LEN/DEX and the number of prior lines of treatment. It can be argued that in situations when the PH assumption is not met, the HR can be interpreted as an average of the HRs that would be calculated for each time point. Even in the Latimer DSU report they mention this interpretation: “In addition, recensoring may lead to biased estimates of the “average” treatment effect in circumstances where proportional treatment effect assumptions do not hold, because longer term data on the effect of treatment may be lost.”	characteristics. Therefore even if the ERG do not feel strongly for either of these mixed and indirect comparison methods, we believe that MAIC is the least biased and the source of our preferred values for relative effectiveness.
22	“It was not clear to the ERG why the submission had considered the set of results for the full trial sample in the PANO/BTZ/DEX arm of PANORAMA-1, in addition to the results for the subpopulation in their subgroup analysis rather than the three sets of results for the subpopulation of 2-3 prior regimens alone, nor how population with at least one prior line of treatment results should be	N/A	Novartis's intention was to use all the data available. All the seven methods investigated serve the only purpose of providing HRs for PFS and OS when comparing LEN/DEX and PAN/BTZ/DEX in the restricted setting (i.e. after at least 2 prior lines of treatment including an IMID and BTZ) where no data is available on LEN/DEX.	No issue of factual accuracy identified.

	interpreted in the context of the full trial sample results presented in the full trial sample analysis." – Section 6.2.2.1, page 152			
23	"Median OS derived from the model of 26.2 months or 2.18 years compares with mean survival of 2.29 years or 27.46 months." - section 6.1.2.3, page 144	N/A	Novartis believes it would be more accurate using the undiscounted figures instead of the discounted when comparing with reported KM figures.	No issue of factual accuracy identified, however the point has some validity. P144 the text has been amended: "Median OS derived from the model of 26.2 months or 2.18 years **corresponds in the model with a mean survival of 2.43 years (undiscounted) or 27.46 months. Although, the ERG have validated the median OS, it should be noted that the company do not give an explanation on how the median OS was derived."**
24	"(...) does not explain the rationale for not including time to next treatment (as an outcome measure included in the scope)." - section 3.4, page 30	N/A	Time to next treatment was not available from the trial data. PANORAMA-1 protocol expected reporting of either progression or initiation of the next treatment. Data on the time of initiation of next treatment therefore is limited.	No issue of factual accuracy identified.
25	"The Kaplan-Meir curves are wrongly titled and refer to subgroup analysis (Group 1) and not to full set." - section	N/A	As per our intention, it refers to the fact that the patients with prior IMID and BTZ treatments were selected from the full analysis set.	No issue of factual accuracy identified.

	4.2.7, page 70			

Issue 3 Correction

	Description of problem	Description of proposed amendment	Justification for amendment	ERG response
26	Data not marked CiC: Section 6.1.2.3, page 144, page 145; section 6.1.2.9, page 151; section 6.3.1.1, page 160;	Mark as CiC	Data are CiC	CiC has been updated accordingly.

References

Latimer, NR. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011.

Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching (2014).

Therneau TM, Grambsch PM. Modeling Survival Data: Extending the Cox Model2000, Springer.

Panobinostat (Farydak®) for treating multiple myeloma in people who have received at least one prior therapy

Erratum

Report commissioned by:

NHS R&D HTA Programme

On behalf of:

NICE

Produced by:

Optimity Advisors
Peninsula Technology Assessment Group (PenTAG)

Although Optimity Advisors are primarily responsible for the work in this report, PenTAG retains responsibility for the standard of the report and the quality of the advice that it contains.

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Declaration of competing interest of the authors

None

Rider of responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows

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Contribution of authors

Adeline Durand: Contributed to project management, the critique of the company's submission, report writing and editing.
Ketevan Rtveladze: Contributed to the critique of the company's submission, report writing and editing.
Clive Pritchard: Contributed to the critique of the company's submission, report writing and editing.
Chris Cooper: Commented on the searches provided by the company and contributed to report writing.
Ruben Mujica-Mota: Contributed to the critique of the company's submission and commented on drafts of the report and is the guarantor of the report from PenTAG.

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Contents

This document contains errata in respect of the ERG report in response to the company's factual inaccuracy check.

The table below lists the location of the change in the original ERG report and the nature of the change.

Page no.	Change
2	The ERG added an acknowledgement.
14	The ERG marked the OS HR in the subgroup of people who had at least 2 prior lines of treatment using Naïve comparison, Unadjusted Cox, and MAIC methods as CIC in Section 1.2.
15	As above
15	Novartis has requested a text around indirect method (MAIC) to be changed. The text has been amended for clarity.
25	Novartis has requested a text around the use of BTZ based regimen in the 3rd line to be changed. The ERG had amended the text and added a paragraph: **"According to the reimbursement algorithm, if a patient has BTZ at induction, then either LEN (NCDF funded) or BTZ (TA129) can be used in the 2nd line. If BTZ is used as 2nd line, then the patient would receive LEN/DEX (TA171). The combination of PANO/BTZ/DEX can then be used instead (as 3rd line). According to our clinical expert, a medical decision could be made to use BTZ in 3rd line therapy after BTZ/DEX induction and LEN as 2nd line, which goes beyond the reimbursement decision. Then the combination of PANO/BTZ/DEX could be used instead as 3rd line."**
27	Novartis has requested a text around the number of patients eligible for PANO use to be changed. The company pointed out the section of the submission where the calculation was presented. The text has been amended accordingly.
32	Novartis has requested a text around the literature searches to be changed as the literature search was within the 6 months limit in line with the guidance. The text has been amended.
52	Novartis clarified that the number patients analysed for the PFS was cited incorrectly in their submission. The ERG has changed the text: "The ERG **was** not clear why the results for PFS **were** only reported for 381 patients instead of 387 for the treatment arm and 377 patients instead of 381 for the control arm. **Following the Factual Error Check, Novartis clarified that PFS analysis was actually conducted for the full analysis set i.e. 387 and 377 for the treatment arm and control arm, respectively."**
56	As above. Sentence has been deleted: **"Once again, the ERG is not clear why the results for PFS are only reported for 381 patients instead of 387 for the treatment arm and 377 patients instead of 381 for the control arm"**.
91	The company requested the text to be amended around HRQL data use in the analysis. The text has been amended accordingly.
92	Novartis has requested a text around indirect method (MAIC) to be changed. The text has been amended for clarity.
123	Marking added to median age at diagnosis is 73.1 years in Section 5.2.3.1
142	Figure 31 label d) and e) relabelled as a) and b).

143	As above
144	Novartis stated that using the undiscounted figures instead of the discounted when comparing with reported KM figures could be more accurate. The ERG has changed the text accordingly.
151	Table 68: The Median treatment duration of the subpopulation of patients who had received at least two prior lines of treatment including thalidomide only and bortezomib based regimen should be 4.8 months. Additionally, the source should say: Adapted from Appendix 17 Table 28
172	Novartis pointed out that Table 88 and 90 showed incorrect data. These tables have been amended accordingly.
173	As above
174	Probabilistic results added Table 94 in Section 7.4.2.4 and wording "**The ERG ran a PSA with these new parameters. The probabilistic ICER £[redacted]. The 95% CIs around key model outcomes are presented in Table 94 below:"**

1. Summary

The text cited directly from the submission by Novartis (hereafter referred to as "the submission") is presented with quotation marks in italic and cross referenced. Note that the specific sections/pages of the submission referred to by the ERG in this report apply to v0.2 of the submission. In addition, the ERG reviewed the economic analysis presented in the Appendix 17 of the submission.

Given the nature of the STA process, the ERG was bound to time constraints. Most of the initial review process was dedicated to finding the methodological and logical errors in the submission and its' Appendix 17. Some updated figures were submitted by the company during the clarification stage.

1.1. Scope of the submission

The submission from Novartis considered the use of panobinostat (Farydak®) in combination with, bortezomib and dexamethasone for people with multiple myeloma who have received at least 1 prior therapy (PANO/BTZ/DEX). The comparator considered was bortezomib and dexamethasone ((placebo)/BTZ/DEX).

Novartis also considered in the Appendix 17 of the submission the use of PANO/BTZ/DEX triplet for patients with relapsed and refractory multiple myeloma who had at least two prior lines of treatment including immunomodulatory drug (IMiD) and BTZ based regimens. The comparator for this analysis was lenalidomide in combination with dexamethasone (LEN/DEX).

1.2. Summary of submitted clinical effectiveness evidence

The clinical effectiveness evidence of the submission is based on the PANORAMA-1 trial that is a phase 3, multicentre, randomised, double-blind, placebo-controlled study in patients with rrMM who have received between one and three prior treatment regimens. In this trial patients received either the triplet therapy PANO/BTZ/DEX or BTZ/DEX. The primary efficacy endpoint of the trial was progression free survival. An extension of 3.9 months was demonstrated (according to investigator assessment). The secondary efficacy endpoints include overall survival, response rate, response duration and time to progression. No mature overall survival results are presented in the submission.

The clinical effectiveness evidence for patients who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen relies on indirect comparison of the PANORAMA-1 trial (the intervention arm) and the pooled data from MM-009 and MM-010 trials for LEN/DEX. The indirect treatment methodology used to estimate the relative effectiveness between PANO/BTZ/DEX and LEN/DEX treatments was the Unadjusted Cox regression. The hazard ratios generated were 1.061 and 1.075 for progression free survival and overall survival, respectively; no confidence intervals were estimated by the company. The company also provided the results of indirect comparisons using naïve comparisons

(HR 1.190 and 0.959 for PFS and OS, respectively), and the matching adjusted indirect comparison method (HR 1.108 and 1.413 for PFS and OS, respectively, which, **compared with the other methods, made a more comprehensive adjustmen**t for baseline differences across treatment groups.

1.3. Summary of submitted cost effectiveness evidence

The cost-effectiveness systematic review of the literature undertaken by Novartis identified 14 studies. The quality assessment was carried out for only six studies out of 14. They compared effectiveness and cost-effectiveness of various treatment options for relapsed or relapsed and refractory multiple myeloma. The modelling approaches of these studies informed the structure of their model.

Novartis developed two cost-utility models as decision analytic semi-Markov model. The structure of the model for the economic analysis of the full PANORAMA-1 trial population (i.e. people who have received at least one prior therapy) includes two pre-progression health states, two post-progression health states and the death health state.
The model for the economic analysis of the subgroup of people who have received at least two prior therapies including IMiD and BTZ regimen includes two pre-progression health states, one post-progression health state and the death health state.

Both models are reported to capture the three key aspects of multiple myeloma that are affected by disease progression and the effects of treatment, namely survival, health related quality of life and costs.

Novartis model produced an ICER for PANO/BTZ/DEX triplet compared to BTZ/DEX of £79,025 cost per QALY gained for the full trial sample analysis of people who have received at least one prior therapy. The probability of PANO/BTZ/DEX being cost-effective at the £30,000 threshold was 0%.

In the subgroup of those patients with ≥2 prior therapies, including IMiD and BTZ, the ICER of PANO/BTZ/DEX vs LEN/DEX was £[redacted] and £[redacted] per QALY gained for subcutaneous and intravenous BTZ administration, respectively

1.4. Commentary on the robustness of submitted evidence

1.4.1. Strengths

- The economic models comparing PANO/BTZ/DEX with BTZ/DEX, in the full trial population, and PANO/BTZ/DEX with LEN/DEX in subgroup of people who had at least 2 prior lines for treatment

that THAL induction is based on a trial, but in practice, most people will receive BTZ/DEX as induction treatment. This, however, contradicts the company's claim based on BCSH guidance that many UK patients receive THAL based therapy at induction (page 38).

Following the induction, patients who are eligible go through high dose chemotherapy (ASCT). Following the ASCT, patients who have a relapse of typically 18 months – 2 years can receive ASCT again. Patients who have a shorter remission or are no longer suitable for ASCT for any other reasons will receive LEN/DEX treatment, which is the relapse setting.

Moreover, the company note that usage of PANO along with bortezomib (BTZ) and dexamethasone (DEX) provides another treatment option for MM. The ERG sought the views of an expert on use of different medications on different lines. It was explained that if a patient had THAL at the 1st line and then relapsed, BTZ/DEX could be used in the 2nd line. The combination of PANO/BTZ/DEX could be then be used instead if superior to BTZ/DEX (as2nd line). If the patient had BTZ at induction, then LEN in the 2nd line can be used (NCDF funded).

According to the reimbursement algorithm, if a patient has BTZ at induction, then either LEN (NCDF funded) or BTZ (TA129) can be used in the 2nd line. If BTZ is used as 2nd line, then the patient would receive LEN/DEX (TA171). The combination of PANO/BTZ/DEX can then be used instead (as 3rd line). According to our clinical expert, a medical decision could be made to use BTZ in 3rd line therapy after BTZ/DEX induction and LEN as 2nd line, which goes beyond the reimbursement decision. Then the combination of PANO/BTZ/DEX could be used instead as 3rd line.

who have received between one and three prior treatment regimens". However, the following section 4.3.2 describes the inclusion criteria of the PANORAMA-1 trial as "*patients with relapsed or relapsed and refractory MM who had received one to three previous treatments".* Also in Section 5.1.1 on page 136 the company mention "*a systematic review was performed in August 2013 to identify economic evidence relating to second-line therapy of patients with rrMM"*. This occurs in several instances throughout the submission.

Therefore the ERG is generally concerned with the confusion that this creates for the PANO indication. The ERG believe that rrMM makes reference to the subgroup analysis of patients who had received at least 2 prior lines of treatment including an IMiD and a BTZ based regimen (the Appendix 17 of the submission).

Our clinical expert however, pointed to the fact that when clinicians talk of rrMM they typically mean relapsed, relapsed and refractory and primary refractory MM as defined in the paper published in Rajkumar et al.[1]

Novartis may also confuse the reader on page 11 of the Appendix 17 of the submission where they analyse the patients who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen which state that the "*economic analysis presented in this Appendix considers patients with relapsed or relapsed and refractory MM who had at least two prior lines of treatment including an IMiD and a bortezomib based regimen".*

The company also note that approximately 1300 patients in England and Wales would be eligible to receive PANO annually **– a title of the paragraph 2 on page 41. The figure is calculated from the HMRN data and equals to 1348 patients. The detailed calculation is only presented later on in Section 6 of the submission.**

The company state that there is a lack of epidemiological data specific to patients with rrMM, but that figures are available for the number of people with MM. Based on CRUK figure, there were 4039 diagnoses in England in 2011 (4792 diagnoses in the UK). Again, it is not really clear why Novartis refer to rrMM population that is defined as the group that had two prior lines of treatment.

Novartis also stated that 37% of patients with MM in England survived cancer for 5 years or more[2]. However, the ERG found more up-to-date figures. Net 5 year survival in England and Wales was 47%[3]. The company cite "*5 year or more survival*" in England in the period of 2005-09 that is 37% from the .

[1] Rajkumar SV, Harousseau JL, Durie B et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Blood 2015:117;15:4691-5.

[2] Cancer Research UK. Myeloma survival statistics. Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/myeloma/survival/ (Accessed 17 June 2014).

[3] Cancer Research UK. Myeloma survival statistics. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/survival#heading-Zero (Accessed 9 July 2015).

The brand name Farydak (sometimes spelt Faridak) was omitted in the company literature searches. The ERG clarified the rationale for this omission and the company replied that the omission has not impacted on the identification of relevant studies. The ERG ran scoping searches to test this point and reached a similar conclusion.

Within the submission, the company observe the paucity of mature trial data and, we note, is aware of further data that is now available to them. In view of additional data being available the ERG asked the company to update their literature searches. The company declined to do so.

In principal, the search syntax and search protocol was adequate to meet the requirements of this submission. We note, however, that the literature searches are now seven months old.

4.1.1.2 Indirect and mixed treatment comparisons

Separate searches for indirect and/or mixed treatment comparators were not undertaken for this submission. The ERG notes however that the range of comparators used in the literature searching is broader than required in the scope.

4.1.1.3 AEs

Separate searches for AEs were not undertaken for this submission. The ERG clarified the rationale for this decision and the company responded that they were aware of all the AE data for PANO.

Given the noted AE profile, the ERG would still have preferred that separate searches were conducted to look beyond one study which has driven this submission.

4.1.1.4 HRQL

Systematic searches were undertaken to identify utility and health related quality of life data. In total, two searches were made.

Search one (2003-2013) took the following form:

1. (terms for myeloma) AND
2. (terms for QLQ-C30, EQ-5D, time trade off etc.,)

Search two (2013-2014) took the following form:

1. (terms for myeloma) AND
2. (terms for QLQ-C30, EQ-5D, time trade off etc.,)
3. (terms for thalidomide or bortezomib or lenalidomide or pomalidomide or carfilzomib or ixazomib or panobinostat)

Literature searches were carried out in MEDLINE, MEDLINE in Process and EMBASE all via OVID. The searches were limited to human-only populations and to studies published in English.

One of the main commentary of the ERG is the use of terms relapsed and relapsed and refractory multiple myeloma. The ERG is generally concerned with the confusion that this creates for the PANO indication. The ERG believe that rrMM makes reference to the subgroup population analysis of patients who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen.

Additionally, according to the final NICE scope, time to next treatment was one of the outcomes to be analysed. However, Novartis do not give a valid explanation why it was excluded.

The ERG is generally concerned with absence of stopping rule that is the UK practice at cycle 4. As noted before, this rule was not implemented in the PANORAMA-1 trial and patients continued treatment up to cycle 12. Moreover, as noted by the company "*there is a notable difference between the way bortezomib was administered in PANORAMA-1 compared with current UK practice"*. Patients do not continue BTZ treatment beyond cycle 8 in the UK. Although this was implemented in the modelling approach as the model allows for 10% of the population to continue treatment beyond cycle 8 (this is further discussed in Section 5.1.2).

4.2 Summary of submitted evidence

The company present the analysis of the efficacy outcomes from PANORAMA-1 trial at the data cut-off of 10 September 2013 and OS data at the data cut-off of 18 August 2014. On page 135 they state that the further trial data would become available in May/June 2015.

The ERG sought clarification information on final trial data. Novartis stated the final OS data is planned to be published in December at the 57th ASH Congress, should the required number of events happened in time for data submission.

4.2.1 Progression free survival

The company present the PFS results as the primary outcome from PANORAMA-1.

In Table 11 we report the results at the data cut-off of 10 September 2013 as per investigator assessment, as per independent review, as well as the multivariate Cox model analysis. As noted in Section 4.1.5, the ERG has clarified that final PFS analysis was performed at the first data cut off (September 2013) since 467 PFS events were recorded at that time.

The ERG **was** not clear why the results for PFS **were** only reported for 381 patients instead of 387 for the treatment arm and 377 patients instead of 381 for the control arm. **Following the Factual Error Check, Novartis clarified that PFS analysis was actually conducted for the full analysis set i.e. 387 and 377 for the treatment arm and control arm, respectively.**

Subgroup	Event, %	Median PFS (95% CI), months	Cox model HR (95% CI), Log-rank p value
PANO/BTZ/DEX	*54.5*	*12.25 (9.46 to 14.62)*	*0.66 (0.50 to 0.86)*
PBO/BTZ/DEX	*70.7*	*8.54 (7.72 to 10.41)*	
Two or three prior lines of therapy			
PANO/BTZ/DEX	*52.6*	*11.99 (9.46 to 13.70)*	*0.64 (0.50 to 0.83)*
PBO/BTZ/DEX	*66.2*	*7.62 (6.01 to 8.67)*	
Prior BTZ use			
PANO/BTZ/DEX	*58.0*	*11.04 (8.34 to 13.70)*	*0.58 (0.44 to 0.77)*
PBO/BTZ/DEX	*68.9*	*7.56 (5.88 to 7.89)*	
No prior BTZ use			
PANO/BTZ/DEX	*50.0*	*12.48 (10.18 to 14.16)*	*0.68 (0.53 to 0.87)*
PBO/BTZ/DEX	*67.8*	*8.64 (7.98 to 10.84)*	

BTZ, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; PANO, panobinostat; PBO, placebo; PFS, progression-free survival.

Source: Submission Table 15

Additionally an analysis of PFS results according to baseline characteristics. In most pre-specified subgroups considered PFS results favoured for the PANO group versus (vs.) the control group. It should be noted that the CI of the HR are crossing 1 for the subgroups: other ethnic origin, no previous use of IMiD drugs, Americas as geographical regions, pooled regions, normal risk of cytogenetic. However, none of the p values of the pre-specified subgroups considered are statically significant.

4.2.2 Response

The overall response rate is relatively similar for patients treated with PANO/BTZ/DEX vs. placebo/BTZ/DEX: 60.7% and 54.6%; p = 0.09. However, the proportion of patients achieving a CR or nCR was approximately two-fold higher in the PANO/BTZ/DEX group than in the placebo/BTZ/DEX group: 27.6% vs. 15.7%; p = 0.00006.

Results from a landmark analysis of data from PANORAMA-1 showed that patients achieving CR/nCR had a longer median PFS compared to patients achieving PR in both treatment groups for each time point evaluated.

Table 14: Landmark analysis for PFS response according to response status in the PANORAMA-1

Landmark time and treatment group	Number of patients		Median PFS after landmark time, months		HR (95% CI)
	with CR/nCR	with PR	Patients with CR/nCR	Patients with PR	
6 weeks					
PANO/BTZ/DEX	*12*	*57*	*NE*	*12.55*	*0.33 (0.12 to 0.89)*
PBO/BTZ/DEX	*3*	*57*	*15.80*	*10.18*	*0.85 (0.19 to 3.90)*
12 weeks					
PANO/BTZ/DEX	*49*	*107*	*16.49*	*10.32*	*0.40 (0.25 to 0.65)*
PBO/BTZ/DEX	*23*	*122*	*14.13*	*9.69*	*0.62 (0.36 to 1.07)*

The use of the terms relapsed, and relapsed and refractory multiple myeloma create some confusion. The ERG is generally concerned with the impact that this may have when considering the evidence provided for the different PANO indications.

The ERG is also concerned with the efficacy data used for the control arm since the use of BTZ does not correspond with that recommended in NICE guidance and will impact on the clinical outcomes from the model. Firstly, there is no 4-cycle stopping rule for the BTZ/DEX arm in the PANORAMA-1 trial as per recommended in the NICE TA129 guidance. Secondly, patients continued treatment up to cycle 16 instead of cycle 8 as per BTZ label. This would have an impact on the clinical outcomes from the model.

The HRQL was not measured in PANORAMA-1 trial during TFI therefore it was necessary **to extrapolate from the last cycle of treatment (full trial sample analysis) or use the utility reported in Acaster et al. (subgroup analysis)**.

Critique on efficacy outcomes:

- There are also a few issues with the reported PFS and OS. Different numbers were observed by investigator and independent review and Novartis do not provide an explanation to this. Additionally, the ERG is not clear why the results for PFS are only reported for 381 patients instead of 387 for the treatment arm and 377 patients instead of 381 for the control arm as they claim that final PFS was observed;
- The company also present a summary of sensitivity analysis around PFS, but no details on parameter change were presented;
- Importantly, no mature OS data for the PANORAMA-1 trial have been reported in this submission.

Novartis present three subgroup population in the submission, but does not make a reference to the third group until the later stage where the indirect and mixed comparison methods are discussed, which serves as a basis for subgroup analysis of patients who had at least 2 prior lines of treatment including an IMiD and a BTZ based regimen.

One of the weaknesses of the clinical effectiveness evidence for the PNAO vs. LEN comparison is that there is no direct trial-based comparison between Len and the primary comparators defined in the scope, therefore the submission relies on indirect comparison.

Critique on the indirect and mixed treatment comparisons (Section 4.10):

- This section appears in the submission without any explanation of how it relates to the effectiveness and cost-effectiveness of PANO in relation to the main incremental analysis for the population of interest. It could be interpreted as indicating that BTZ/DEX is an inappropriate comparator of PANO/BTZ/DEX for some patients who have received at least one prior therapy. This warrants further discussion given that the authorised indication for PANO has yet to be determined;
- Novartis compare results of the duration of exposure and TTP/PFS reported from various trials with different comparators, however the ERG would like to insist that there might be many confounding

factors between the populations considered within these different trials therefore a direct comparison is not appropriate;

- Generally, the methods of indirect and mixed comparisons are poorly described. Novartis do not give many details on the methods used. The ERG is concerned with absence of the WinBUGS files as the company claimed that is what they have used for the common comparison method;
- A number tables in the section on indirect and mixed comparisons have errors and statistical significance is no systematically presented;
- Most importantly, all the evidence arising from these studies is likely to be affected by confounding, whether it is from observed differences across trials and trial arms in baseline characteristics, or unmeasured confounding. **Analyses unadjusted or partially adjusted** for baseline differences are likely to be biased (including the analyses using individual patient data, which also invalidly assume proportional hazards) **and those based on the MAIC method** suffer from low statistical power (as evidenced by the effective sample sizes).

starting ages in the model given that, in the UK, nearly 60% of patients are estimated to be diagnosed at the age of 70 or older and the median age at diagnosis is **73.1** years. This compares with a starting age in the model of 62.1 years.

5.2.3.2 Clinical effectiveness data

Most of the effectiveness data for the full trial sample analysis in the economic model was drawn from PANORAMA-1. The one exception is that progression data for those receiving LEN/DEX after failure to the initial treatment came from MM-009 and MM-010 as data for progression in patients receiving subsequent antineoplastic treatment after PANO/BTZ/DEX or BTZ/DEX was not collected in the PANORAMA-1 trial.

The health states between which patients move in the model were defined in terms of progression or non-progression of illness. The risk of progression or death in a given cycle was modelled by fitting survival functions to Kaplan-Meier plots of patient level PFS data. Because the risk of progression and the risk of death were both required by the model, the proportion of patients who progressed relative to those who had a PFS event (death or disease progression) was estimated for each cycle by a logistic regression. The model appears to follow the structure set out in the, as we have described in Section 5.1.2.2, although a more intuitive explanation of how the health states presented in Figure 37 in the submission correspond to the labels used in the excel model.

A similar survival analysis approach was adopted to the risk of treatment discontinuation. The modelled survival functions appeared to be implemented appropriately and transition probabilities similarly derived from the survival functions using standard methods.[4]

The fitting of survival functions to the observed data has not been replicated as part of this critique as the ERG have not had access to patient-level data from PANORAMA-1, MM-009 or MM010. Neither have the ERG replicated the results of the indirect treatment comparisons analysis. However, the following section makes some observations on the differences between the modelled survival estimates used in the cost-effectiveness calculations and the survival observed in PANORAMA-1.

In Section 7, we explored the impact on the ICER if patients were not required to discontinue BTZ therapy despite having less than minimal response at cycle 4, as per PANORAMA-1 trial, in order to reflect the efficacy used in the control arm of the model.

5.2.3.3 Mortality data

Modelled survival in the cost-effectiveness analysis should mimic the observed survival in PANORAMA-1 as all the mortality data in the full trial sample model, including for patients who proceed to LEN/DEX after PANO/BTZ/DEX or BTZ/DEX (although data on progression in this group was not collected as part of PANORAMA-1 and is based on MM-009 and MM-010 studies), is drawn from the trial.

The ERG noted that the modelled mean survival in the PANO group was greater than the median survival reported by PANORAMA-1 at the 18th August 2014 interim analysis (mean of 42.84 vs. median of 38.24 months) but that the reverse was true fort the PBO group (mean of 33.56 vs. a median of 35.38 months).

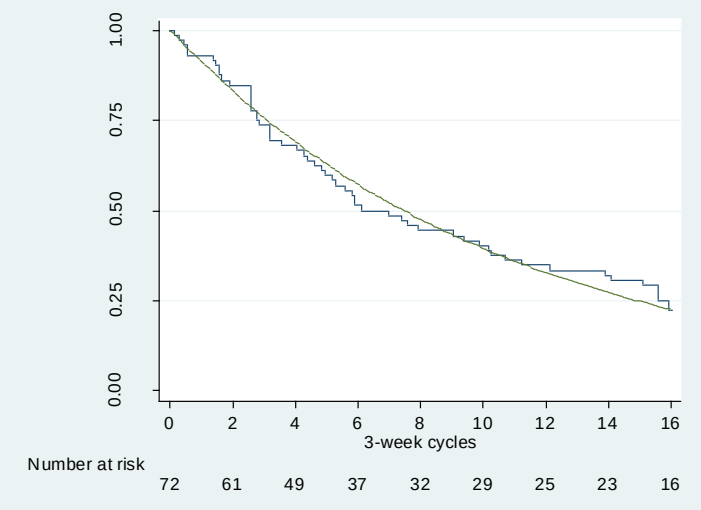
[4] Latimer, N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011.

PANO/BTZ/DEX (four sets of results for an equal number of different indirect comparison methods applied to the full trial sample and three to the subpopulation with two or three prior lines of treatment). It was assumed that these HRs were applicable to the subgroup under investigation (the subpopulation with at least two prior lines of treatment including IMiD and BTZ). It was not clear to the ERG why the submission had considered the set of results for the full trial sample in the PANO/BTZ/DEX arm of PANORAMA-1, in addition to the results for the subpopulation in their subgroup analysis rather than the three sets of results for the subpopulation of 2-3 prior regimens alone, nor how population with at least one prior line of treatment results should be interpreted in the context of the full trial sample results presented in the full trial sample analysis.

The transition probabilities for risk of treatment discontinuation were derived in the same way as for the risk of progression or pre-progression death. The same five parametric survival models were fitted to treatment discontinuation data from the PANORAMA-1 trial using the safety analysis set of patients (72 patients). Subsequently, AIC and BIC values are provided to justify the use of the exponential distribution to be the best fitting model amongst the five tested for discontinuation while on PANO/BTZ/DEX. The exponential model was considered the best model for BTZ/DEX responders. The Kaplan-Meier plots and fitted models are reported in Figure 31 below.

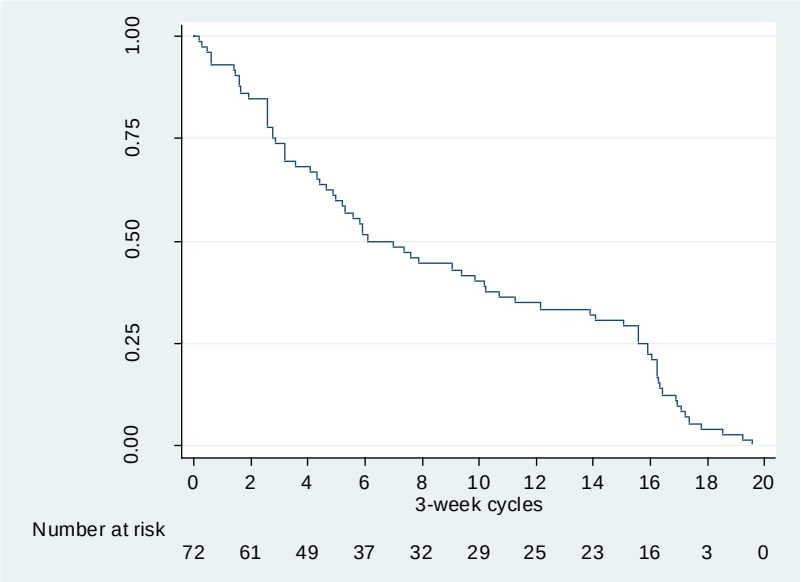
Figure 31: Proportion of patients without treatment discontinuation: subpopulation with prior IMiD and BTZ and ≥ 2 prior lines of treatment; a) Kaplan–Meier curve and fitted parametric models (PANO/BTZ/DEX – exponential model) for 48 weeks b) Kaplan–Meier curve presenting full follow-up data

a) PANO/BTZ/DEX – exponential model (48 weeks)



Source: Appendix Figure 4a)

b) PANO/BTZ/DEX – full follow up data



BTZ, bortezomib; DEX, dexamethasone; IMiD, immunomodulatory drug; PANO, panobinostat.
Source: Appendix Figure 4 a) and 4 b)

For the LEN/DEX group, unlike PFS and OS, treatment discontinuation cannot be compared between the two treatment regimens using indirect treatment comparisons because LEN/DEX is a continuous treatment. Comparing the median PFS and median treatment duration for the PANORAMA-1 full trial population (11.1 and 10.1 months) and the PANORAMA-1 subpopulation with two or three prior lines of treatment (9.5 and 9.2 months), it was assumed that the risk of treatment discontinuation for the full trial sample is 9.9% higher (11.1/10.1) than the risk of PFS in each model cycle and 3.3% higher (9.5/9.2) in the subpopulation.

Table 62 below summarises the approaches used to derived transition probabilities and their use in the model.

Table 62: Approaches used to derived transition probabilities and their use in the economic model

Parameter	*Data source*	*Model used for base case*	*Use of transition probabilities*
PANO/BTZ/DEX			
Risk of progression or death	*PANORAMA-1, PANO/BTZ/DEX arm Patient-level PFS data*	*Weibull*	*Pre-progression, Tx1, PANO/BTZ/DEX*
Risk of treatment discontinuation	*PANORAMA-1, PANO/BTZ/DEX arm Patient-level treatment duration data*	*Exponential*	*Pre-progression, Tx1, PANO/BTZ/DEX*
Risk of death	*PANORAMA-1, PANO/BTZ/DEX arm Patient-level OS data*	*Gompertz*	*Post-progression (derived as OS-PFS) PANO/BTZ/DEX*
Risk of experiencing adverse events	*PANORAMA-1, PANO/BTZ/DEX arm Patient-level AE data*	*Occurrence probability*	*Pre-progression, Tx1, PANO/BTZ/DEX*
LEN/DEX[a]			
Risk of progression or pre-progression death (relative to PANO/BTZ/DEX)	*Simulated patient level data from MM-009/010, published Kaplan–Meier plot for PFS*	*Hazard ratio*	*Pre-progression, Tx1, LEN/DEX*

Parameter	Data source	Model used for base case	Use of transition probabilities
Risk of treatment discontinuation	*Median PFS and median treatment duration published for MM-009/010*	*Hazard ratio*	*Pre-progression, Tx1 PANO/BTZ/DEX*
Risk of death (relative to PANO/BTZ/DEX)	*Simulated patient level data from MM-009/010, published Kaplan–Meier plot for PFS*	*Hazard ratio*	*Post-progression, Tx1 (derived as OS-PFS) LEN/DEX*

[a] For LEN/DEX, to keep the model parsimonious, exponential distribution was applied.

AE, adverse event; BTZ, bortezomib; DEX, dexamethasone; LEN, lenalidomide; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; Tx, treatment.

San Miguel et al. 2013[5], Dimopoulos et al 2009[6], Stadtmauer et al 2009[7]

Source: Novartis submission, Appendix 17 Table

For OS, the Kaplan-Meier curves and the fitted Gompertz distribution for PANO/BTZ/DEX patients in the subgroup of ≥2 prior therapies did not display the divergence between the actual and predicted outcomes observed for the full PANORAMA-1 trial sample, as shown in Figure 32 (compare this with Figure 26). In the subgroup analysis, the model underestimates PFS compared with the clinical trial results for patients people who have received at least 2 previous treatments including an IMiD and BTZ receiving PANO/BTZ/DEX (12 months vs. 12.5 months). Modelled OS is also underestimated compared with the clinical trial (26.2 months vs. [redacted] months). Median OS derived from the model of 26.2 months or 2.18 years **corresponds in the model with a mean survival of 2.43 years (undiscounted) or 27.46 months. Although, the ERG have validated the median OS, it should be noted that the company do not give an explanation on how the median OS was derived.** The median survival figures are presented in Table 72 of this report. As PFS and OS for LEN/DEX were derived from the indirect treatment comparison, it was not possible to compare the Kaplan-Meier curves with the modelled data. Median survival was not reported for patients receiving LEN/DEX, while mean survival was 2.22 years derived from the full trial population data using MAIC approach. The mean survival based on Unadjusted Cox method using the subpopulation data was 2.19 years. Details of the MAIC and Unadjusted Cox approaches for indirect treatment comparisons are given in Section 4.3 of this report.

[5] San Miguel J, Weisel K, Moreau P et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. The Lancet oncology 2013;14:1055–66.

[6] Dimopoulos MA, Chen C, Spencer A et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia 2009;23:2147–52.

[7] Stadtmauer EA, Weber DM, Niesvizky R et al. Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma. Eur J Haematol 2009;82:426–32.

Table 68: Clinical data for subgroup populations

Outcome	*Clinical trial result (Prior IMiD, BTZ and ≥ 2 LoT)*	*Clinical trial result (Prior IMiD, BTZ and ≥ 2 LoT including THAL only and BORT)*
Median PFS (PANO/BTZ/DEX)	*12.5 months*	*12.5 months*
Median OS (PANO/BTZ/DEX)	[redacted] *months*	[redacted] *months*
Median treatment duration (PANO/BTZ/DEX)	*4.2 months*	***4.8** months*

Source: Adapted from Appendix 17 Table 28

Other limitations are described by Novartis:

- Post-progression treatments have not been reported for LEN/DEX therefore the impact of difference in the post-progression treatments (between PANO/BTZ/DEX vs. LEN/DEX) on survival could not be assessed;
- there was a mismatch between the efficacy data from Dimopoulos et al. 2009[8], Stadtmauer et al. 2009[9] for the combined MM-009/010 trial data, used for the indirect treatment comparisons, and the data used for the treatment costs of LEN/DEX (TA171 NICE Guidance based on the European MM-010 trial only);
- four-weekly cost of LEN/DEX were rescaled to 3-weekly cost, which may also introduce some bias;
- there may be some double counting of terminal care costs as it is not clear from the study of Gooding et al whether end of life care costs were included in their study or not. Novartis claim that because the difference between the OS profiles of the PANO/BTZ/DEX and LEN/DEX is minor, the inclusion or exclusion of terminal care costs has a negligible impact on the results.

6.1 Critique of approach used

6.2.1. Critique of the modelling approach and structure

The structure of the model constructed by Novartis for the subgroup analysis appeared to be logical and had greater clarity than the full trial sample model in terms of the treatment of death and the correspondence between the two arms of the model (PANO/BTZ/DEX and LEN/DEX). The model followed the structure set out in Figure 29. The model structure and health states are justified with respect to previous models, including those developed for NICE submissions. The health states included in the model are the same as in the model presented by Novartis for the analysis of full PANORAMA-1 trial sample with the exception that there is no transition to the state LEN+DEX. Transition probabilities have been estimated using standard methods and the probabilities for the transitions in each time period sum to one.

Key features of the analysis are justified with reference to previous cost-effectiveness models and NICE's guide to the methods of technology appraisals. One aspect of the model design which is not justified is the choice of comparators. While the relevance of LEN/DEX as a comparator for

[8] Dimopoulos MA, Chen C, Spencer A et al. Long-term follow-up on overall survival from the MM–009 and MM–010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia 2009;23 2147–52.

[9] Stadtmauer EA, Weber DM, Niesvizky R et al. Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma. Eur J Haematol 2009;82:426–32.

Table 87: Base-case ICER if HRs estimated using the Naïve comparison method – intravenous BTZ administration

Methodology	*Technologies*	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£) versus LEN/DEX*	*Incremental LYG versus LEN/DEX*	*Incremental QALYs versus LEN/DEX*	*ICER (£) Cost per Lys gained*[a]	*ICER (£) Cost per QALYs gained*[a]
'Naïve comparison' deriving HRs from full trial populations	*PANO/BTZ/DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*0.009*	*-0.0066*	*£[redacted]*	*[redacted]*
	LEN/DEX	*£155,466*	*2.279*	*1.527*					
''Naïve comparison' deriving HRs from subpopulation (2 to 3 prior lines)	*PANO/BTZ/DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*-0.061*	*-0.0465*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£163,203*	*2.348*	*1.567*					

Source: Produced by the ERG

Table 88 Base-case ICER if HRs estimated using the Naïve comparison method – subcutaneous BTZ administration

Methodology	*Technologies*	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£) versus LEN/DEX*	*Incremental LYG versus LEN/DEX*	*Incremental QALYs versus LEN/DEX*	*ICER (£) Cost per Lys gained*[a]	*ICER (£) Cost per QALYs gained*[a]
'Naïve comparison' *deriving HRs from full trial populations*	*PANO/BTZ/DEX*	***£[redacted]***	*2.288*	*1.521*	***£[redacted]***	***0.009***	***-0.007***	*[redacted]*	***£[redacted]***
	LEN/DEX	***£155,466***	***2.279***	***1.527***					
'Naïve comparison' *deriving HRs from subpopulation (2 to 3 prior lines)*	*PANO/BTZ/DEX*	***£[redacted]***	*2.288*	*1.521*	*£[redacted]*	*-0.061*	*-0.0465*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£163,203*	*2.348*	*1.567*					

Source: Produced by the ERG

Hazard ratios estimated using the Unadjusted Cox method

The ERG re-run the model using the Unadjusted Cox method to estimate the HRs for PFS and OS for the full trial population only since this method was used for the subgroup of patients with 2 to 3 prior lines of therapy in the base case.

Table 89: Base-case ICER if HRs estimated using the Unadjusted Cox method – intravenous BTZ administration

Methodology	*Technologies*	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£) versus LEN/DEX*	*Incremental LYG versus LEN/DEX*	*Incremental QALYs versus LEN/DEX*	*ICER (£) Cost per Lys gained*[a]	*ICER (£) Cost per QALYs gained*[a]
'Unadjusted Cox' deriving HRs from full trial populations	*PANO/BTZ/DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*-0.004*	*-0.0230*	*[redacted]*	*[redacted]*
	LEN/DEX	*£152,456*	*2.292*	*1.544*					

Source: Produced by the ERG

Table 90: Base-case ICER if HRs estimated using the Unadjusted Cox method – subcutaneous BTZ administration

Methodology	*Technologies*	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£) versus LEN/DEX*	*Incremental LYG versus LEN/DEX*	*Incremental QALYs versus LEN/DEX*	*ICER (£) Cost per Lys gained*[a]	*ICER (£) Cost per QALYs gained*[a]
***'Unadjusted Cox'** deriving HRs from full trial populations*	*PANO/BTZ/DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*-0.004*	*-0.023*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£152,456*	*2.292*	*1.544*					

Source: Produced by the ERG

Hazard ratios estimated using the MAIC method

The ERG re-run the model using the MAIC method to estimate the HRs for PFS and OS for the group of patients with 2 to 3 prior lines of therapy only since this method was used for the full trial population in the base case.

We found that this amendment would decrease the ICER of 18% from £[redacted] to £[redacted] for intravenous BTZ administration and increase the ICER of 38% from £[redacted] to £[redacted] for subcutaneous BTZ administration.

Table 91: Base-case ICER if HRs estimated using the MAIC method – intravenous BTZ administration

Methodology	*Technologies*	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£) versus LEN/DEX*	*Incremental LYG versus LEN/DEX*	*Incremental QALYs versus LEN/DEX*	*ICER (£) Cost per Lys gained*[a]	*ICER (£) Cost per QALYs gained*[a]
'MAIC' deriving HRs from subpopulation (2 to 3 prior lines)	*PANO/BTZ/DEX*	*£[redacted]*	*2.288*	*1.521*	*£[redacted]*	*0.461*	*0.2839*	*£[redacted]*	*£[redacted]*
	LEN/DEX	*£120,148*	*1.827*	*1.237*					

Source: Produced by the ERG

Table 92: Base-case ICER if HRs estimated using the MAIC method – subcutaneous BTZ administration

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
MAIC' deriving HRs from subpopulation (2 to 3 prior lines)	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.2839	0.461	£[redacted]	£[redacted]
	LEN/DEX	£120,148	1.827	1.237					

Source: Produced by the ERG

The ERG believe that this indirect comparison may be the preferred option to estimate the relative effectiveness between LEN/DEX and PANO/BTZ/DEX. The generated ICER for the subcutaneous administration of BTZ is £[redacted]. However, as explained in more details in Section 6.2.2.2 the MAIC estimates are likely to be unreliable and biased by unobserved confounding.

In addition the ERG re-run the model using the MAIC method with the cost of Lymphopenia set at a zero instead of £167; and the specialist visit frequency at every 2nd cycle instead of every cycle, the

Table 93: Base-case ICER if HRs estimated using the MAIC method with updated specialist visit frequency and zero cost of Lymphopenia – subcutaneous BTZ administration

Methodology	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) versus LEN/DEX	Incremental LYG versus LEN/DEX	Incremental QALYs versus LEN/DEX	ICER (£) Cost per Lys gained[a]	ICER (£) Cost per QALYs gained[a]
MAIC' deriving HRs from subpopulation (2 to 3 prior lines)	PANO/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.2839	0.461	£[redacted]	£[redacted]
	LEN/DEX	£120,108	1.827	1.237					

Source: Produced by the ERG

The ERG believe that the generated ICER for the subcutaneous administration of BTZ of £[redacted] is the most plausible ICER for patients with 2 to 3 prior lines of therapy.

The ERG ran a PSA with these new parameters. The probabilistic ICER £[redacted]. The 95% CIs around key model outcomes are presented in Table 94 below:

Table 94: Values and 95% confidence intervals for the ERG's preferred assumptions

	Cost	Mean incremental cost	QALYs	Incremental QALY	ICER
PANO/BTZ/DEX	£[redacted] (£[redacted] to £[redacted])	£[redacted] (£[redacted] to £[redacted])	1.521 (1.051 to 2.142)	0.257 (–0.451 to 0.820)	£[redacted]
LEN/DEX	£120,108 (£52,266 to £241,099)		1.237 (0.678 to 2.180)		

Source: Produced by the ERG

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2009

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Farydak® (panobinostat) for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.

3.2 Please outline the rationale for developing the patient access scheme.

It is to provide a cost-effective therapy to the NHS, thereby facilitating access to patients with relapsed or relapsed and refractory multiple myeloma.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

Simple Patient Access Scheme offering a price for the product that is lower than the list price.

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

It is to be applied to the whole licenced population of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The Scheme would be applied without any restrictions or criteria applied.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

100% of those receiving the treatment.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The scheme will operate as a fixed price scheme (which will not vary with any change to the UK list price). The confidential PAS price will be applied directly on the original invoice produced by Novartis to the purchasing organisation.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

Each NHS Trust will be informed of the PAS price by Novartis Pharmaceuticals UK Ltd in the form of a PAS letter. The scheme does not increase administrative burden to the NHS.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

The Scheme does not have any specific requirement. The confidential PAS price will be applied directly on the original invoice produced by Novartis to the purchasing organisation. The scheme does not increase administrative burden to the NHS.

3.10 Please provide details of the duration of the scheme.

The patient access scheme might be stopped if Novartis Pharmaceuticals UK Ltd decides to adjust the UK list price for panobinostat, so that the list price is the same as or less than that under this proposed patient access scheme.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

No

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

Each NHS Trust will be informed of the PAS price by Novartis Pharmaceuticals UK Ltd in the form of a PAS letter. (Please see Appendix A)

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

N/A

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

The submitted economic model accomodates any level of potential discount.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The level of discount applied on the list price of the drug can be specified in Cell "F41" on the "Model Settings" sheet. Corrections to some of the cost calculations have been made during clarification.[1]

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

A simple discount is considered as PAS. Neither the clinical input data, nor the submitted model is changing when applying the PAS.

[1] Corrections of the cost calculations described in the manufacturer's response to the NICE Clarification Questions (clarification questions B9):

- The administration cost (whether intravenous or subcutaneous) related to BTZ was wrongly calculated by being multiplied with the dose intensity of BTZ (75.8%).
- 3-weekly monitoring cost related to PAN/BTZ/DEX was wrongly calculated by double-counting the cost of the specialist visit (£156).
- The dose intensity was updated based on PANORAMA-1 trial data applicable to the licensed restricted population (after at least two prior treatments including an IMID and BTZ)

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

Table 1 Costs associated with the implementation and operation of the patient access scheme (PAS)

	Calculation of cost	Reference source
Stock management	£0	N/A
Administration of claim forms	£0	N/A
Staff training	£0	N/A
Other costs…	£0	N/A
…		
…		
Total implementation/ operation costs	£0	N/A

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Table 2 Additional treatment-related costs for the intervention both with and without the patient access scheme (PAS) [2]

[2] With the factual errors corrected as described in the manufacturer's response to the NICE/ERG clarification questions B9.

a) During treatment Phase I (cycles 1-8) assuming intravenous (IV) administration for BTZ

	Intervention without PAS		Intervention with PAS[3]		Reference source
	Unit cost (£)	**Total cost per 3 weeks cycle (£)**	**Unit cost (£)**	**Total cost per 3 weeks cycle (£)**	
Panobinostat	£776.00	£3,552.53	£[redacted]	£[redacted]	Assumption, PANORAMA-1
Bortezomib	£512.54	£1,517.11	£512.54	£1,517.11	BNF, PANORAMA-1
Dexamethasone	£7.80	£49.80	£7.80	£49.80	BNF, PANORAMA-1
Administration	£156.00	£624.00	£156.00	£624.00	National schedule of reference costs (2013-2014)
AE management	£136.85	£136.85	£136.85	£136.85	National schedule of reference costs (2013–2014); NICE TA316;
Monitoring	£185.56	£185.56	£185.56	£185.56	National schedule of reference costs (2013-2014); NICE TA312; NICE TA338; NICE cg176;
Total treatment-related costs		£6,065.85		£[redacted]	

PAS: patient access scheme.

[3] A simple discount of [redacted]% has been approved by DH

b) During treatment Phase II (cycles 9-16) assuming intravenous (IV) administration for BTZ

	Intervention without PAS		Intervention with PAS[4]		Reference source
	Unit cost (£)	**Total cost per 3 weeks cycle (£)**	**Unit cost (£)**	**Total cost per 3 weeks cycle (£)**	
Panobinostat	£776.00	£3,552.53	£[redacted]	£[redacted]	Assumption, PANORAMA-1
Bortezomib	£512.54	£758.56	£512.54	£758.56	BNF, PANORAMA-1
Dexamethasone	£7.80	£24.90	£7.80	£24.90	BNF, PANORAMA-1
Administration	£156.00	£312.00	£156.00	£312.00	National schedule of reference costs (2013-2014)
AE management	£136.85	£136.85	£136.85	£136.85	National schedule of reference costs (2013–2014); NICE TA316;
Monitoring	£185.56	£185.56	£185.56	£185.56	National schedule of reference costs (2013-2014); NICE TA312; NICE TA338; NICE cg176;
Total treatment-related costs		£4,970.40		£[redacted]	

PAS: patient access scheme.

[4] A simple discount of [redacted]% has been approved by DH

c) During treatment Phase I (cycles 1-8) assuming subcutaneous (SC) administration for BTZ

	Intervention without PAS		Intervention with PAS[5]		Reference source
	Unit cost (£)	**Total cost per 3 weeks cycle (£)**	**Unit cost (£)**	**Total cost per 3 weeks cycle (£)**	
Panobinostat	£776.00	£3,552.53	£[redacted]	£[redacted]	Assumption, PANORAMA-1
Bortezomib	£512.54	£1,517.11	£512.54	£1,517.11	BNF, PANORAMA-1
Dexamethasone	£7.80	£49.80	£7.80	£49.80	BNF, PANORAMA-1
Administration	£25.00	£100.00	£25.00	£100.00	National schedule of reference costs (2013-2014)
AE management	£136.85	£136.85	£136.85	£136.85	National schedule of reference costs (2013–2014); NICE TA316;
Monitoring	£185.56	£185.56	£185.56	£185.56	National schedule of reference costs (2013-2014); NICE TA312; NICE TA338; NICE cg176;
Total treatment-related costs		£5,541.85		£[redacted]	

PAS: patient access scheme.

[5] A simple discount of [redacted]% has been approved by DH

d) During treatment Phase II (cycles 9-16) assuming subcutaneous (SC) administration for BTZ

	Intervention without PAS		Intervention with PAS[6]		Reference source
	Unit cost (£)	**Total cost per 3 weeks cycle (£)**	**Unit cost (£)**	**Total cost per 3 weeks cycle (£)**	
Panobinostat	£776.00	£3,552.53	£[redacted]	£[redacted]	Assumption, PANORAMA-1
Bortezomib	£512.54	£758.56	£512.54	£758.56	BNF, PANORAMA-1
Dexamethasone	£7.80	£24.90	£7.80	£24.90	BNF, PANORAMA-1
Administration	£25.00	£50.00	£25.00	£50.00	National schedule of reference costs (2013-2014)
AE management	£136.85	£136.85	£136.85	£136.85	National schedule of reference costs (2013–2014); NICE TA316;
Monitoring	£185.56	£185.56	£185.56	£185.56	National schedule of reference costs (2013-2014); NICE TA312; NICE TA338; NICE cg176;
Total treatment-related costs		£4,708.40		£[redacted]	

PAS: patient access scheme.

Summary results

Base-case analysis[7]

4.7 Please present in separate tables the cost-effectiveness results as follows.[8]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

[6] A simple discount of [redacted]% has been approved by DH
[7] Please see results under 4.8
[8] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 3 Base-case cost-effectiveness results

a) Without PAS assuming intravenous (IV) administration for BTZ

	PAN/BTZ/DEX	LEN/DEX
Intervention cost (£)	£45,360	£40,724
Post progression treatment costs (£)	£[redacted]	£100,598
Adverse event cost (£)	£1,155	£191
Total costs (£)*	£[redacted]	£147,632
Difference in total costs (£)	N/A	£[redacted]
LYG	2.29	2.19
LYG difference	N/A	0.10
QALYs	1.52	1.47
QALY difference	N/A	0.052
ICER (£/QALY)	N/A	£[redacted]

**Also including monitoring cost.*

b) With PAS[9] assuming intravenous (IV) administration for BTZ

	PAN/BTZ/DEX	LEN/DEX
Intervention cost (£)	£[redacted]	£40,724
Post progression treatment costs (£)	£[redacted]	£100,598
Adverse event cost (£)	£1,155	£191
Total costs (£)*	£150,989	£147,632
Difference in total costs (£)	N/A	£3,357
LYG	2.29	2.19
LYG difference	N/A	0.10
QALYs	1.52	1.47
QALY difference	N/A	0.052
ICER (£)	N/A	£64,819

**Also including monitoring cost.*

[9] A simple discount of [redacted]% has been approved by DH

c) Without PAS assuming subcutaneous (SC) administration for BTZ

	PAN/BTZ/DEX	**LEN/DEX**
Intervention cost (£)	££41,679	£40,724
Post progression treatment costs (£)	£[redacted]	£100,598
Adverse event cost (£)	£1,155	£191
Total costs (£)*	£[redacted]	£147,632
Difference in total costs (£)	N/A	£[redacted]
LYG	2.29	2.19
LYG difference	N/A	0.10
QALYs	1.52	1.47
QALY difference	N/A	0.052
ICER (£/QALY)	N/A	£[redacted]

**Also including monitoring cost.*

d) With PAS[10] assuming subcutaneous (SC) administration for BTZ

	PAN/BTZ/DEX	**LEN/DEX**
Intervention cost (£)	£[redacted]	£40,724
Post progression treatment costs (£)	£[redacted]	£100,598
Adverse event cost (£)	£1,155	£191
Total costs (£)*	£147,308	£147,632
Difference in total costs (£)	N/A	-£324
LYG	2.29	2.19
LYG difference	N/A	0.10
QALYs	1.52	1.47
QALY difference	N/A	0.052
ICER (£)	N/A	dominant

**Also including monitoring cost.*

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

[10] A simple discount of [redacted]% has been approved by DH

4.8 Please present in separate tables the incremental results as follows. [11]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

Table 4 Base-case incremental results

a) Intravenous (**IV**) BTZ administration assumed ***without*** **PAS**

Methodology: 'Unadjusted Cox' deriving HRs from subpopulation (2 to 3 prior lines)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LY)	ICER (£/QALY)
PAN/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.102	0.0518	£[redacted]	£[redacted]
LEN/DEX	£147,632	2.186	1.469					

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; BTZ: bortezomib ; PAN : panobinostat ; DEX : dexamethasone ; LEN : lenolidomide.

b) Intravenous (**IV**) BTZ administration assumed ***with*** **PAS**[12]

Methodology: 'Unadjusted Cox' deriving HRs from subpopulation (2 to 3 prior lines)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LY)	ICER (£/QALY)
PAN/BTZ/DEX	£150,989	2.288	1.521	£3,357	0.102	0.0518	£32,999	£64,819
LEN/DEX	£147,632	2.186	1.469					

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; BTZ: bortezomib ; PAN : panobinostat ; DEX : dexamethasone ; LEN : lenolidomide.

[11] For outcome-based schemes, please see section 5.2.9 in appendix B.

[12] A simple discount of [redacted]% has been approved by DH

c) Subcutaneous (**SC**) BTZ administration assumed ***without*** **PAS**

Methodology: 'Unadjusted Cox' deriving HRs from subpopulation (2 to 3 prior lines)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LY)	ICER (£/QALY)
PAN/BTZ/DEX	£[redacted]	2.288	1.521	£[redacted]	0.102	0.0518	£[redacted]	£[redacted]
LEN/DEX	£147,632	2.186	1.469					

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; BTZ: bortezomib ; PAN : panobinostat ; DEX : dexamethasone ; LEN : lenolidomide.

d) Subcutaneous (**SC**) BTZ administration assumed ***with*** **PAS**[13]

Methodology: 'Unadjusted Cox' deriving HRs from subpopulation (2 to 3 prior lines)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LY)	ICER (£/QALY)
PAN/BTZ/DEX	£147,308	2.288	1.521	-£324	0.102	0.0518	dominant	dominant
LEN/DEX	£147,632	2.186	1.469					

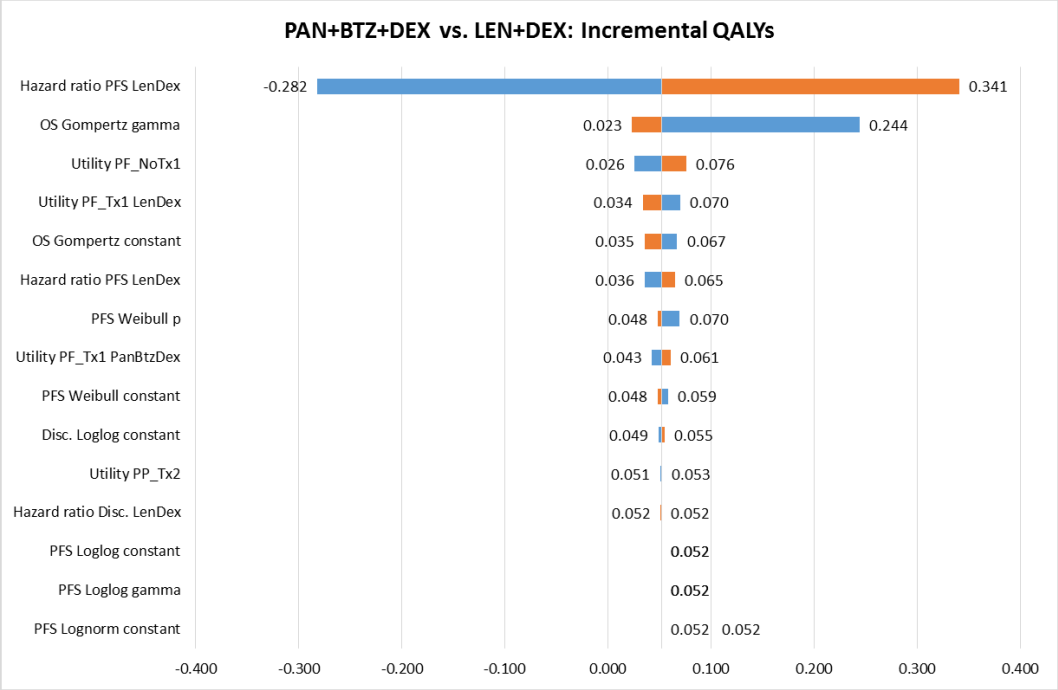
LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; BTZ: bortezomib ; PAN : panobinostat ; DEX : dexamethasone ; LEN : lenolidomide.

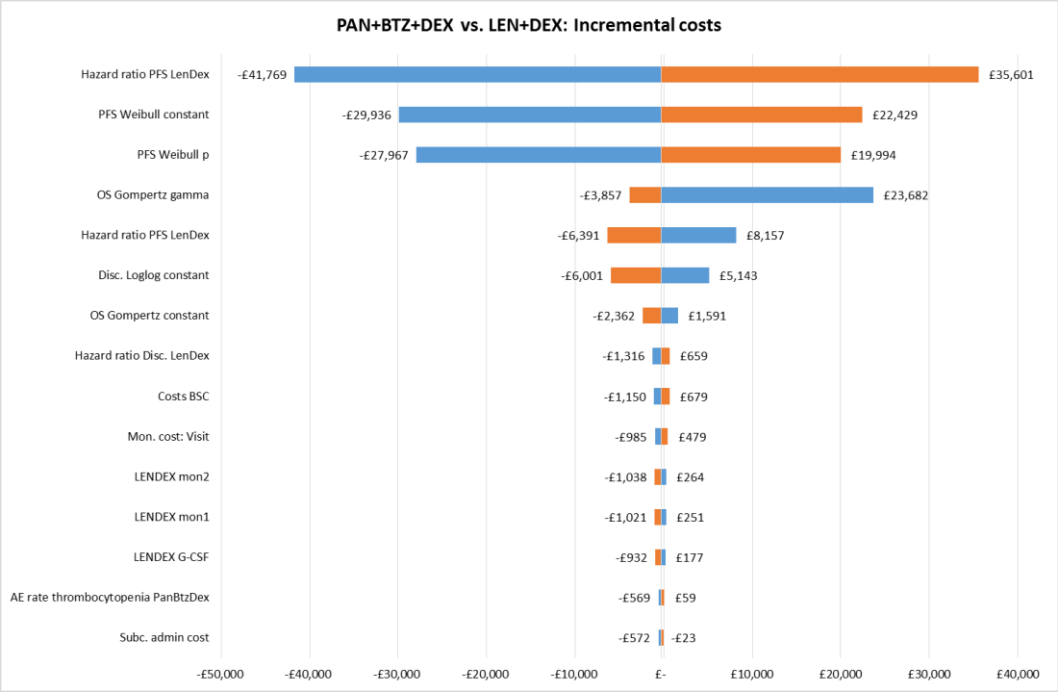
Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Methodology: 'Unadjusted Cox' deriving HRs from subpopulation (2 to 3 prior lines) assuming subcutaneous (SC) administration of BTZ with PAS[714]

[13] A simple discount of [redacted]% has been approved by DH
[14] A simple discount of [redacted]% has been approved by DH


PAN+BTZ+DEX vs. LEN+DEX: Incremental QALYs
Hazard ratio PFS LenDex
OS Gompertz gamma
Utility PF_NoTx1
Utility PF_Tx1 LenDex
OS Gompertz constant
Hazard ratio PFS LenDex
PFS Weibull p
Utility PF_Tx1 PanBtzDex
PFS Weibull constant
Disc. Loglog constant
Utility PP_Tx2
Hazard ratio Disc. LenDex
PFS Loglog constant
PFS Loglog gamma
PFS Lognorm constant
-0.282
0.341
0.023
0.244
0.026
0.076
0.034
0.070
0.035
0.067
0.036
0.065
0.048
0.070
0.043
0.061
0.048
0.059
0.049
0.055
0.051
0.053
0.052
0.052
0.052
0.052
0.052
0.052
-0.400
-0.300
-0.200
-0.100
0.000
0.100
0.200
0.300
0.400


PAN+BTZ+DEX vs. LEN+DEX: Incremental costs
Hazard ratio PFS LenDex
PFS Weibull constant
PFS Weibull p
OS Gompertz gamma
Hazard ratio PFS LenDex
Disc. Loglog constant
OS Gompertz constant
Hazard ratio Disc. LenDex
Costs BSC
Mon. cost: Visit
LENDEX mon2
LENDEX mon1
LENDEX G-CSF
AE rate thrombocytopenia PanBtzDex
Subc. admin cost
-£41,769
£35,601
-£29,936
£22,429
-£27,967
£19,994
-£3,857
£23,682
-£6,391
£8,157
-£6,001
£5,143
-£2,362
£1,591
-£1,316
£659
-£1,150
£679
-£985
£479
-£1,038
£264
-£1,021
£251
-£932
£177
-£569
£59
-£572
-£23
-£50,000
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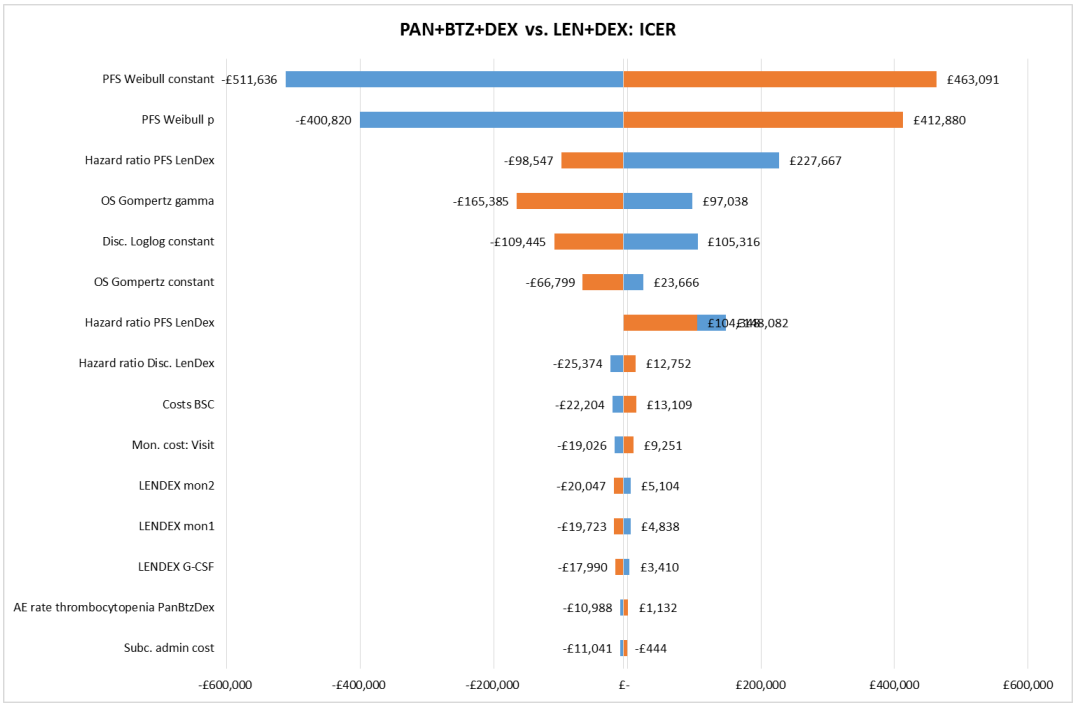
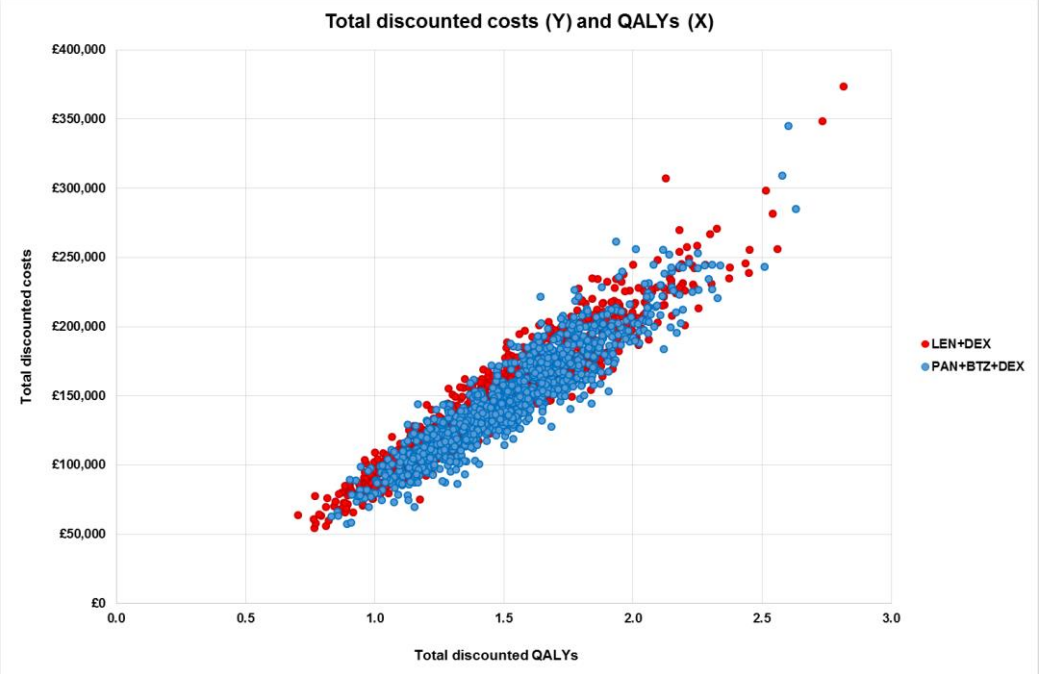
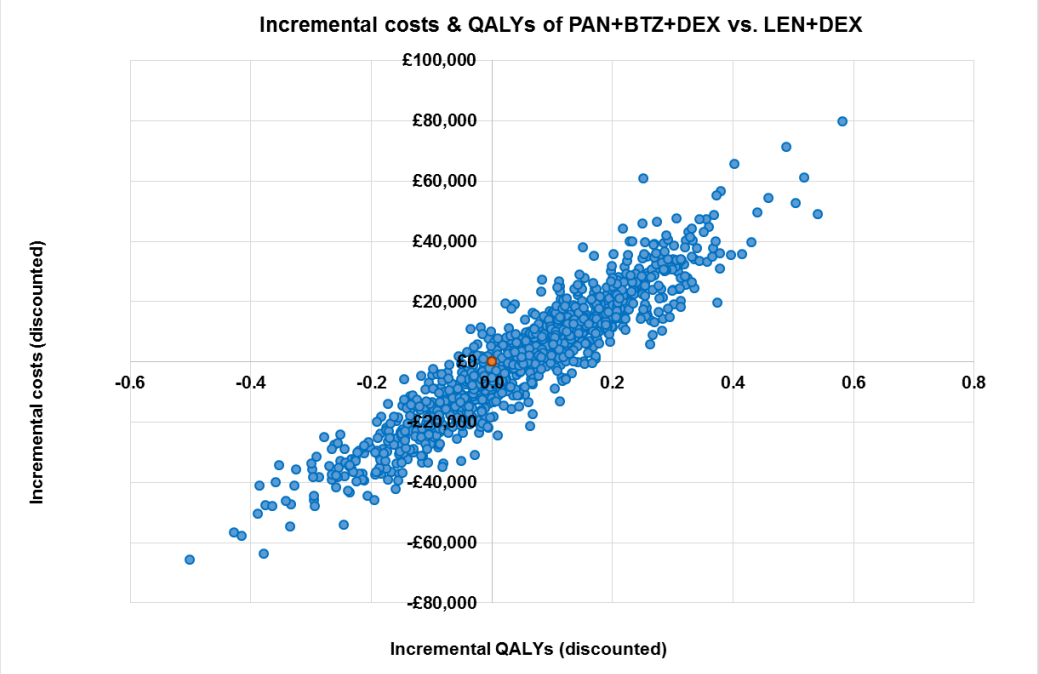
£-
£10,000
£20,000
£30,000
£40,000


PAN+BTZ+DEX vs. LEN+DEX: ICER
PFS Weibull constant
-£511,636
£463,091
PFS Weibull p
-£400,820
£412,880
Hazard ratio PFS LenDex
-£98,547
£227,667
OS Gompertz gamma
-£165,385
£97,038
Disc. Loglog constant
-£109,445
£105,316
OS Gompertz constant
-£66,799
£23,666
Hazard ratio PFS LenDex
£104,348,082
Hazard ratio Disc. LenDex
-£25,374
£12,752
Costs BSC
-£22,204
£13,109
Mon. cost: Visit
-£19,026
£9,251
LENDEX mon2
-£20,047
£5,104
LENDEX mon1
-£19,723
£4,838
LENDEX G-CSF
-£17,990
£3,410
AE rate thrombocytopenia PanBtzDex
-£10,988
£1,132
Subc. admin cost
-£11,041
-£444
-£600,000
-£400,000
-£200,000
£-
£200,000
£400,000
£600,000

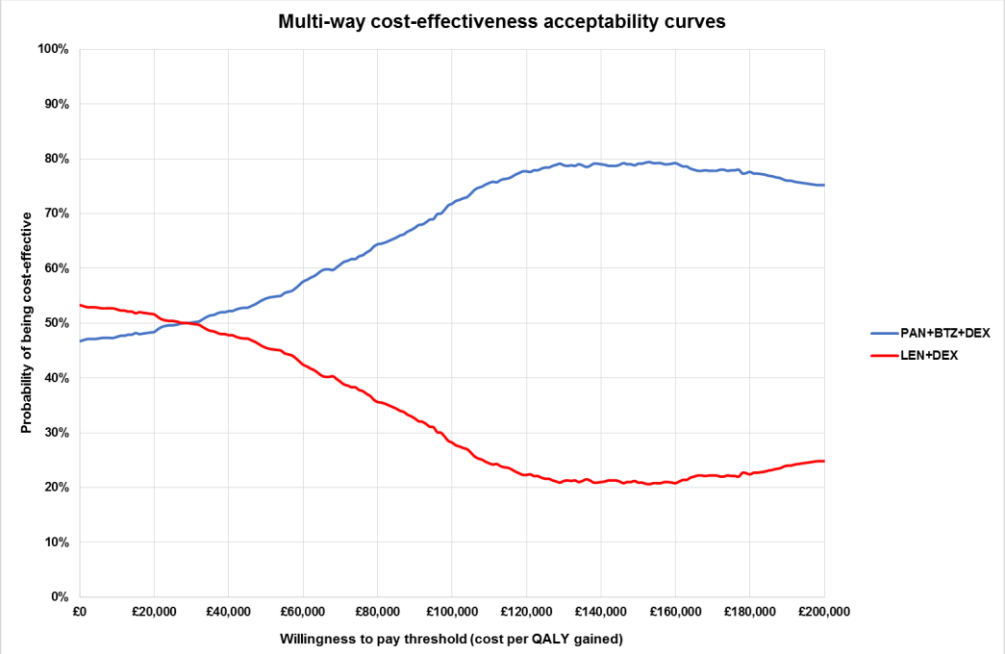
4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

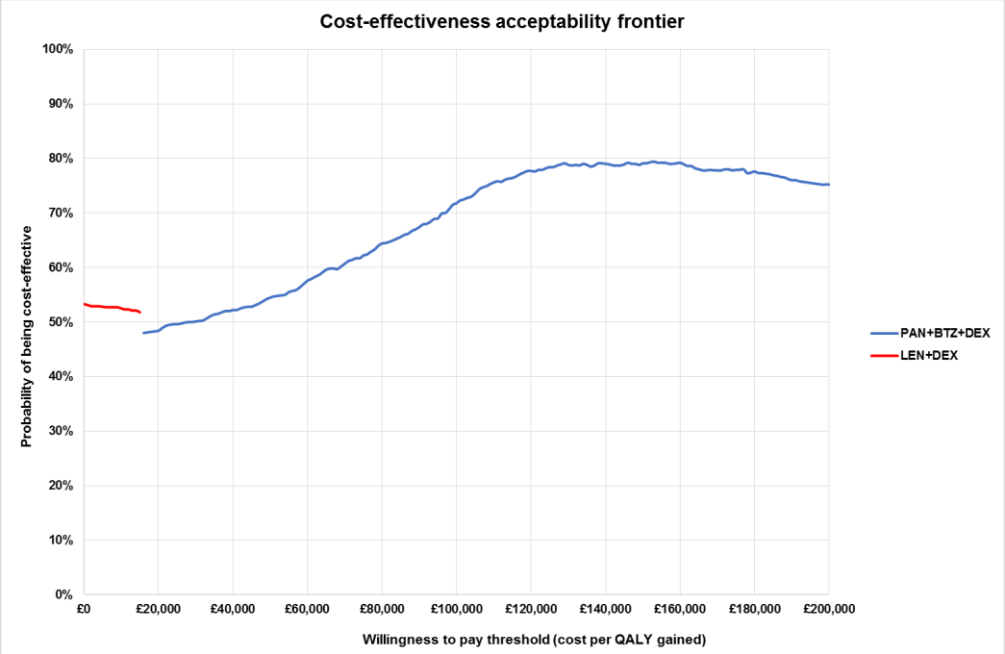
Methodology: 'Unadjusted Cox' deriving HRs from subpopulation (2 to 3 prior lines) assuming subcutaneous (SC) administration of BTZ with PAS[15]





[15] A simple discount of [redacted]% has been approved by DH


Multi-way cost-effectiveness acceptability curves
Probability of being cost-effective
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
£0
£20,000
£40,000
£60,000
£80,000
£100,000
£120,000
£140,000
£160,000
£180,000
£200,000
Willingness to pay threshold (cost per QALY gained)
PAN+BTZ+DEX
LEN+DEX


Cost-effectiveness acceptability frontier
Probability of being cost-effective
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
£0
£20,000
£40,000
£60,000
£80,000
£100,000
£120,000
£140,000
£160,000
£180,000
£200,000
Willingness to pay threshold (cost per QALY gained)
PAN+BTZ+DEX
LEN+DEX

4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

Scenario analysis results presented assuming subcutaneous bortezomib administration, using 'Unadjusted Cox' method deriving HRs from data on subpopulation data of 2 to 3 prior lines applying PAS[16]

- 5% discount rates for costs and effects:

Incremental costs	**Incremental QALYs**	**Incremental LYs**	**ICER (QALYs)**	**ICER (LYs)**
-£431	0.0489	0.097	dominant	dominant

- 5 and 10 years of time horizon:

Incremental costs	**Incremental QALYs**	**Incremental LYs**	**ICER (QALYs)**	**ICER (LYs)**
Time horizon: 5 years				
-£1,375	0.0434	0.089	dominant	dominant
Time horizon: 10 years				
-£324	0.0518	0.102	dominant	dominant

- Overall survival:

Incremental costs	**Incremental QALYs**	**Incremental LYs**	**ICER (QALYs)**	**ICER (LYs)**
Weibull				
£2,368	0.0735	0.136	£32,230	£17,463
Kaplan–Meier + best fitting				
£1,016	0.0626	0.119	£16,236	£8,568

- Progression-free survival:

Incremental costs	**Incremental QALYs**	**Incremental LYs**	**ICER (QALYs)**	**ICER (LYs)**
Gompertz				
-£445	0.0514	0.102	dominant	dominant

- Time to discontinuation:

[16] A simple discount of [redacted]% has been approved by DH

Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
Kaplan–Meier based				
-£559	0.0518	0.102	dominant	dominant

- Distribution of fourth line treatments:

Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
Full PANORAMA-1 population[17]				
-£2,782	0.0518	0.102	dominant	dominant
Prior IMiD population[18]				
-£3,177	0.0518	0.102	dominant	dominant

- Utility associated with LEN/DEX equal to off-treatment

Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
-£324	0.0483	0.102	dominant	dominant

- Results of scenario analysis: various methodologies applied

Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
'Unadjusted Cox' (ITT)				
-£5,148	–0.0230	–0.004	£223,604	£1,233,601
'MAIC' (ITT)				
-£1,258	0.0295	0.071	dominant	dominant
'Naïve' (2 to 3 prior lines of treatment)				
-£15,894	–0.0465	–0.061	£341,896	£262,553

[17] 38.1% LEN/DEX, 6% BTZ/DOX, 21.6% BTZ/THAL/DEX, 29.8% BTZ/CYC/DEX, 4.5% POM/DEX

[18] 34.6% LEN/DEX, 8.6% BTZ/DOX, 23.5% BTZ/THAL/DEX, 33.3% BTZ/CYC/DEX, 0% POM/DEX

- Threshold analyses various HR of PFS for LEN/DEX versus PANO/BTZ/DEX

Incremental costs	Incremental QALYs	Incremental LYs	ICER (QALYs)	ICER (LYs)
HR = 0.8				
£8,059	0.036	0.102	£223,848	£79,225
HR = 0.9				
£4,213	0.043	0.102	£98,040	£41,414
HR = 1				
£1,204	0.049	0.102	£24,707	£11,837
HR = 1.1				
-£1,210	0.054	0.102	dominant	dominant
HR = 1.2				
-£3,191	0.058	0.102	dominant	dominant

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

N/A

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 5 Results showing the impact of patient access scheme on ICERs

	ICER for intervention (PAN/BTZ/DEX) versus:	
	Comparator (LEN/DEX)	
	Without PAS	**With PAS[19]**
Intravenous BTZ; 'Unadjusted Cox' method	£[redacted]	£64,819
Subcutaneous BTZ; 'Unadjusted Cox' method	£[redacted]	dominant

PAS: patient access scheme; BTZ: bortezomib ; PAN : panobinostat ; DEX : dexamethasone ; LEN : lenolidomide.

[19] A simple discount of [redacted]% has been approved by DH

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Response

Hospital Commercial Account Manager
Tel :
Email :

Novartis Pharmaceuticals UK Ltd
Frimley Business Park
Camberley
Surrey
GU16 7SR
01276 698717

Dear XXX,

STRICTLY CONFIDENTIAL
RE: FARYDAK® (panobinostat) PATIENT ACCESS SCHEME ("PAS")

Please find attached details of the PAS available to XXX ("the Trust") in regard to the purchase of FARYDAK® over the duration of TAXXX.

The Trust shall treat all information (including details of pricing and discount levels) ("the Confidential Information") contained in this letter as strictly confidential in accordance with the terms relating to Confidential Information as set out in the NHS Terms and Conditions for the Supply of Goods dated August 2014 ("NHS Conditions").

Product	NHS List Price	PAS Price
FARYDAK® 10mg x 6 capsules	£3,492.00	£[redacted]
FARYDAK® 15mg x 6 capsules	£3,492.00	£[redacted]
FARYDAK® 20mg x 6 capsules	£4,656.00	£[redacted]

All orders will be subject to the Novartis Pharmaceuticals UK Limited's Standard Terms and Conditions of Sale in force from time to time ("Novartis Terms") and should be placed with: Customer Care, Novartis Pharmaceuticals UK Ltd, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR. Tel: 0845 7419442 Fax: 0845 7419443.

The Trust has informed Novartis that the delivery point(s) will be the Pharmacy Department(s) of the following hospitals:

- XXX (inserted by Novartis based on current Trust purchasing points)

Please notify Novartis should these delivery points be inaccurate or you wish to nominate an alternative third party provider to dispense on your behalf.

Yours faithfully

.....
Novartis Pharmaceuticals UK Limited

5.2 Appendix B: Details of outcome-based schemes

5.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Response

5.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

5.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Response

5.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Response

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Response

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

5.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

5.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Panobinostat (Farydak®) for treating multiple myeloma in people who have received at least one prior therapy

A critique of the patient access scheme submission from Novartis

Report commissioned by:

NHS R&D HTA Programme

On behalf of:

NICE

Produced by:

Optimity Advisors
Peninsula Technology Assessment Group (PenTAG)

Although Optimity Advisors are primarily responsible for the work in this report, PenTAG retains responsibility for the standard of the report and the quality of the advice that it contains.

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Declaration of competing interest of the authors

None

Rider of responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

Contribution of authors

Adeline Durand: Contributed to project management, the critique of the company's submission, report writing and editing.
Ketevan Rtveladze: Contributed to the critique of the company's submission, report writing and editing.
Clive Pritchard: Contributed to the critique of the company's submission, report writing and editing.
Chris Cooper: Commented on the searches provided by the company and contributed to report writing.
Ruben Mujica-Mota: Contributed to the critique of the company's submission and commented on drafts of the report and is the guarantor of the report from PenTAG.

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Date completed:

August 2015

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List of abbreviations:

AE	Adverse event
BTZ	bortezomib
CYC	cyclophosphamide
DEX	dexamethasone
DOX	doxorubicin
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
IMiD	immunomodulatory drug
LEN	lenalidomide
LOT	line of treatment
MAIC	matching adjusted indirect treatment comparison
NICE	National Institute for Health and Care Excellence
OS	overall survival
PANO	panobinostat
PANORAMA	Panobinostat Oral in multiple Myeloma
PAS	Patient Access Scheme
PBO	placebo
PFS	progression-free survival
POM	pomalidomide
PSA	Probabilistic sensitivity analysis
QALY	quality-adjusted life years
SD	standard deviation
THAL	thalidomide
WTP	willingness to pay

1. Background

The submission from Novartis considered the use of panobinostat (Farydak®) in combination with, bortezomib and dexamethasone for people with multiple myeloma who have received at least 1 prior therapy (PANO/BTZ/DEX). The comparator considered was bortezomib and dexamethasone ((placebo)/BTZ/DEX).

Novartis also considered in the Appendix 17 of the submission the use of PANO/BTZ/DEX triplet for patients with relapsed and refractory multiple myeloma who had at least two prior lines of treatment including immunomodulatory drug (IMiD) and BTZ based regimens. The comparator for this analysis was lenalidomide in combination with dexamethasone (LEN/DEX).

The patient access scheme (PAS) refers to the subgroup analysis of treating patients with relapsed and refractory multiple myeloma who had at least two prior lines of treatment including IMiD and BTZ.

The ERG was asked by the National Institute for Health and Care Excellence (NICE) to provide the additional critique of the submitted PAS analysis results. A discount of [redacted] has been approved by the Department of Health (DH) and the cost of PANO is decreased from £776 per 20 mg unit (without PAS) to [redacted] per 20 mg unit (with PAS).

Novartis presented updated figures in the PAS document. These will be discussed further in Section 2.

The cost associated with the treatment with and without PAS are presented by phases, i.e. phase 1 cycles 1-8 and phase 2 cycles 9-16. The cost were also presented by BTZ administration method – subcutaneous (SC) or intravenous (IV).

Novartis also present the base-case analysis results for both IV and SC administration of BTZ, with and without the PAS. These will be discussed further in Section 2.

The sensitivity analysis is conducted for a number of inputs assuming SC administration and the new cost of PANO ([redacted] per unit). This report comments on the deterministic sensitivity analysis and the scenario analyses conducted by Novartis using their preferred assumptions and reports the checks carried out by the ERG by running the company's model with the stated sensitivity/scenario analyses. It also comments on the probabilistic sensitivity analysis and presents base case results using the ERG's preferred assumptions and sensitivity analyses around those results.

2. Critique of PAS

2.1. Introduction

Novartis have negotiated a Simple Patient Access Scheme (PAS) with the Department of Health for the provision of PANO. Under the terms of the agreement, PANO will be supplied at a price lower than the list price. The agreed discount of [redacted] reduces the price of PANO from £776 to [redacted] per 20mg capsule. The company's PAS submission present the treatment related cost with and without the PAS. The costs are presented by phases:

- Phase 1: cycles 1-8; and
- Phase 2: cycles 9-16.

Costs are reported per 3-week cycle of PANO and for the total costs of PANO/BTZ/DEX triplet therapy under the assumptions of IV and SC administration of BTZ.

The treatment cost per 3-week cycle of PANO is reduced from £3,552.53 to [redacted] reflecting a [redacted] discount of the PAS.

Total treatment related costs per 3-weekly cycle are reduced from £6,065.85 to [redacted] by applying the PAS for cycles 1-8 assuming IV administration of BTZ. For cycles 9-16, the total treatment related cost is reduced from £4,970.40 to [redacted]. The total treatment related cost takes into account the administration cost, management of the adverse events (AEs) and monitoring costs.

Total treatment related costs per 3-weekly cycle are reduced from £5,541.85 to [redacted] by applying the PAS for cycles 1-8 assuming SC administration of BTZ. For cycles 9-16, the total cost per 3-week cycle is reduced from £4,708.40 to [redacted] by applying the PAS.

All figures were cross-checked and validated by the ERG. The figures were found to be consistent with the model outputs. The per patient treatment cost calculations were found to be consistent with a [redacted] reduction in the acquisition cost of PANO, with other costs held constant.

2.2. Outline of report

The following section reports the ERG's verification of the company's base case estimates of cost-effectiveness with and without the PAS, and under the assumptions of IV or SC administration of BTZ. Since the positive CHMP opinion relates to patients who have received at least two prior lines of therapy including an IMiD and BTZ, this is the group considered in the PAS submission. All the analyses therefore relate to the comparison of PANO/BTZ/DEX with LEN/DEX.

A critical assumption in the company's base case is the use of the Unadjusted Cox to derive hazard ratios from data on the subpopulation who have received at least two prior lines of therapy. Section 2.4 shows the effect of varying this assumption on the company's results, while retaining the company's other baseline assumptions. Section 2.4.2 then presents the base case results for the four options. The ERG's preferred assumptions are then reported in Section 2.4.2, before going on to comment on the company's sensitivity and scenario analyses in Section 2.5.

2.3. Base case results

The base-case analysis presented in the PAS submission reports results for IV and SC administration of BTZ with or without the PAS. Deterministic results for cost, QALYs, life years and cost-effectiveness ratios were therefore presented for four options:

- Without PAS, assuming IV administration of BTZ;
- With PAS, assuming IV administration of BTZ;
- Without PAS, assuming SC administration of BTZ;
- With PAS, assuming SC administration of BTZ

The results for each of these four options are presented in Table 1. Assuming SC administration of BTZ, PANO/BTZ/DEX generates more QALYs than LEN/DEX but its higher cost generates an ICER of [redacted] per QALY gained without the PAS whereas, applying the PAS, PANO/BTZ/DEX remains more effective but is also less costly. The effect of reducing the price of PANO, under base case assumptions, is that PANO/BTZ/DEX dominates LEN/DEX on the basis of the deterministic analysis. This result, assuming SC administration of BTZ, is the company's new base case on which their sensitivity and scenario analyses are based.

Table 1: Company's estimates of cost-effectiveness with intravenous or subcutaneous BTZ and with and without PAS

Option	Without PAS	Intravenous BTZ	Unadjusted Cox: 2-3 prior LOT
Deterministic			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£147,632	[redacted]	[redacted]
QALYs	1.47	1.52	0.05
ICER			[redacted]
PSA results (1 run)			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£152,763	[redacted]	[redacted]
QALYs	1.51	1.55	0.04
ICER			[redacted]
Option	**With PAS**	**Intravenous BTZ**	**Unadjusted Cox: 2-3 prior LOT**
Deterministic			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£147,632	£150,989	£3,357
QALYs	1.47	1.52	0.05
ICER			**£64,819**
PSA results (4 runs)			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£150,525	£154,017	£3,491
QALYs	1.50	1.54	0.05
ICER			**£74,745**

Option	Without PAS	Subcutaneous BTZ	Unadjusted Cox: 2-3 prior LOT
Deterministic			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£147,632	[redacted]	[redacted]
QALYs	1.47	1.52	0.05
ICER			[redacted]
PSA results (3 runs)			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£151,897	[redacted]	[redacted]
QALYs	1.50	1.54	0.04
ICER			[redacted]
Option	**With PAS**	**Subcutaneous BTZ**	**Unadjusted Cox: 2-3 prior LOT**
Deterministic			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£147,632	£147,308	-£324
QALYs	1.47	1.52	0.05
ICER			**dominant**
PSA results (2 runs)			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£149,552	£149,920	£368
QALYs	1.48	1.53	0.05
ICER			**£7,067**

Source: Adapted from Table 4 in PAS

The ERG was able to verify the deterministic results presented in the PAS submission for these four options. Since the implementation of the PAS in the model brings about such a large change in cost-effectiveness, from an ICER well in excess of NICE's threshold of cost-effectiveness, at over £80,000 per QALY gained, to a position where PANO/BTZ/DEX is unambiguously preferred on the basis of the mean deterministic ICER, the ERG also considered the probabilistic cost-effectiveness results.

When there are nonlinearities in the economic model, the mean ICER based on the probabilistic analysis is to be preferred to that based on the deterministic analysis. Differences between deterministic and probabilistic results reported in Table 1 are indicative of nonlinearities in the model. It generally required more than one run of the company's probabilistic sensitivity analysis (PSA) macro to generate a set of results for the PSA as one or more of the 1000 simulations generated an invalid output (i.e. #DIV/0!). This occurred for both costs and QALYs in PANO/BTZ/DEX and LEN/DEX arms of the model, suggesting that, for some variables, the PSA macro may have been selecting from part of the distribution which wouldn't be observed in practice. Each PSA run will produce a different result, The probabilistic ICER that the ERG obtained by running the company's model (with the number of runs required to generate a result given in brackets) was less favourable than the deterministic result (between 14.6% and 21.2% higher for the results presented here). In the company's preferred assumption (i.e. assuming subcutaneous administration of BTZ with PAS) the probabilistic ICER was found positive rather than dominant for PANO/BTZ/DEX.

Of greater concern, however, was the sensitivity of the model results to changes in the method used to generate hazard ratios (HRs). This is explored in the Section below.

2.4. Additional work undertaken by the ERG

2.4.1. Impact of using different indirect comparison methods

In the company's base case analysis under PAS, the key assumption is the use of the Unadjusted Cox method to estimate the relative effectiveness between PANO/BTZ/DEX and LEN/DEX. The company's PAS submission explores the effect of using the Naïve method instead of the Unadjusted Cox in their scenario analyses to derive the HR for LEN/DEX.

Table 2 summarises the HRs for LEN/DEX vs. PANO/BTZ/DEX obtained by the three different indirect treatment comparison methods. It should be noted that the 95% Cis were only provided by the company in the Factual error response for the Unadjusted Cox and Matched Adjusted Indirect Treatment Comparison (MAIC) methods.

Table 2: Summary of the three indirect comparison – subgroup of ≥2 prior lines of therapy

	Naive comparison	*Unadjusted Cox*	*Matching adjusted indirect treatment comparison*
Progression-free survival	*1.190*	*1.061 (0.80 - 1.41)*	*1.108 (0.58 – 2.12)*
Overall survival	*0.959*	*1.075 (0.76 – 1.53)*	*1.413 (0.62 – 3.24)*

Source: Adapted from Submission Table 29b

Table 3 reports the determinist results reported in the PAS submission and compares the costs and effects of PANO/BTZ/DEX and LEN/DEX under the same assumptions used in the PAS submission with the use of the MAIC method (the ERG's preferred assumption).

Table 3: Impact of HR assumption on company's cost-effectiveness estimates (deterministic results)

Base case: Unadjusted Cox			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£147,632	£147,308	-£324
QALYs	1.469	1.521	0.05
ICER			**dominant**
Naïve comparison			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£163,203	£147,308	-£15,894
QALYs	1.567	1.521	-0.0465
ICER			**£341,896**
MAIC			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£120,148	£147,308	£27,161
QALYs	1.237	1.521	0.2839
ICER			**£95,683**

Source: Adapted from PAS Submission using others indirect comparison methods (this change the HRs appropriately)

Although the ERG's preferred HRs (MAIC's for patients with ≥2 prior therapies) are more favourable to PANO/BTZ/DEX than the HRs adopted by the company's base case (Unadjusted cox for patients with ≥2 prior therapies), the resulting ICER for the former case is worse than that for the latter. It may be seen in Table 3 that the increased effectiveness associated with the MAIC estimate, 0.28 vs 0.05 QALYs per patient for MAIC and Unadjusted Cox, respectively, is accompanied by a more than proportional increase in total costs, i.e. to 27,161 from-£324 for MAIC and Unadjusted Cox, respectively.

In the base case result using the Unadjusted Cox, PANO/BTZ/DEX dominates LEN/DEX, that is, it is more effective and less costly. In the Naïve method, LEN/DEX is more effective but at substantially greater cost, with an ICER of over £300,000 per QALY gained. This ICER is qualitatively different than the base case result since in that case, the higher the ICER the more favourable PANO/BTZ/DEX is (i.e. point estimate falls in south west quadrant).Both cases would therefore favour PANO/BTZ/DEX on the basis of NICE's usual cost per QALY threshold.

In contrast, using MAIC generates markedly greater QALYs for PANO/BTZ/DEX compared to LEN/DEX but generates an ICER approaching £100,000 per QALY gained in the deterministic analysis (i.e. point estimate fall in north east quadrant).

2.4.2. Impact of using the ERG assumptions

The most important difference between the ERG's and the company's preferred approach is the use of the MAIC as an indirect comparison to derive the HRs from data on the subpopulation of 2 to 3 prior line of treatments for patients, rather than the Unadjusted Cox method.

Although the ERG believe that the MAIC method is likely to be unreliable and bias due to a low statistical power, it addresses some of the issues that the Unadjusted Cox method do not consider. The Unadjusted Cox method does not control for differences in baseline characteristics and therefore is very likely to add a greater bias than a method which does adjust for or differences between the trials in terms of patient and disease characteristics at baseline.
Therefore we believe that MAIC method is the least biased and the source of our preferred values for relative effectiveness.

Based on our clinical expert's advice, the additional changes made in the ERG analysis compared with that of the company are as follows:

- Lymphopenia set at a zero instead of £167; and
- Specialist visit frequency every 2nd cycle instead of every cycle.

Table 4 reports cost-effectiveness results under the ERG's preferred assumptions noted above across the four options presented in Table 1, namely with and without PAS and with intravenous or subcutaneous BTZ.

Table 4: Cost-effectiveness analysis: ERG's preferred assumptions using MAIC method

Option	Without PAS	Intravenous BTZ	MAIC: 2-3 prior LOT
Deterministic			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£120,108	[redacted]	[redacted]
QALYs	1.24	1.52	0.28

ICER			[redacted]
PSA results (1 run)			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£128,247	[redacted]	[redacted]
QALYs	1.31	1.54	0.22
ICER			[redacted]
Option	**With PAS**	**Intravenous BTZ**	**MAIC: 2-3 prior LOT**
Deterministic			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£120,107.79	£149,990.72	£29,883
QALYs	1.24	1.52	0.28
ICER			**£105,272**
PSA results (2 runs)			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£124,117	£151,613	£27,496
QALYs	1.28	1.53	0.25
ICER			**£111,697**
Option	**Without PAS**	**Subcutaneous BTZ**	**MAIC: 2-3 prior LOT**
Deterministic			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£120,108	[redacted]	[redacted]
QALYs	1.24	1.52	0.28
ICER			[redacted]
PSA results (1 run)			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£125,754	[redacted]	[redacted]
QALYs	1.29	1.54	0.24
ICER			[redacted]
Option	**With PAS**	**Subcutaneous BTZ**	**MAIC: 2-3 prior LOT**
Deterministic			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£120,108	£146,310	£26,202
QALYs	1.24	1.52	0.28
ICER			**£92,306**
PSA results (4 runs)			
	LEN/DEX	PANO/BTZ/DEX	Incremental
Costs	£124,951	£149,032	£24,081
QALYs	1.29	1.54	0.24
ICER			**£99,880**

Source: Produced by the ERG

These results confirm the impact illustrated in Table 3 of using MAIC rather than Unadjusted Cox approach to estimating the HRs. Incorporating the ERG's other preferred assumptions gives a slightly

lower ICER in the deterministic analysis of £92,306 per QALY gained, compared with £95,683 using the company's other preferred assumptions. As in other analyses, the probabilistic ICER that the ERG obtained by running the company's model (with the number of runs required to generate a result given in brackets) was higher than the deterministic result (between 6.1% and 8.7% higher for the results presented here).

2.5. Sensitivity analysis results

A range of sensitivity analyses was provided in Novartis's submission:

- Probabilistic sensitivity analysis;
- Deterministic sensitivity analysis; and
- Scenario analysis.

These are reviewed in depth in Section 2.5.1 below.

2.5.1. Deterministic results

2.5.1.1. Deterministic sensitivity analysis

The ERG have not validated the company's univariate sensitivity analysis. The results of which are presented in the form of tornado diagrams. Little explanation of these is provided either in the company's original submission (where they featured only for the population for whom a positive CHMP opinion has been received) or in the PAS submission. The charts are difficult to interpret as the label 'Hazard ratio PFS LenDex' appears in each chart in two places. Nevertheless, the results appear to show that varying the parameters which govern overall and progression-free survival between upper and lower confidence limits can have a substantial impact on the differences in QALYs and costs generated by the model for the two treatment arms. For example, the tornado on the ICER shows a range of ICERs from -£511,636 to £463,091 when one of the parameters describing the Weibull model of PFS is varied between its 95% confidence limits. When compared with these findings, the impact on costs and QALYs of basing the model's hazard functions on MAIC rather than the Unadjusted Cox method do not appear to be implausibly large. While the tornado diagram gives an indication of the sensitivity of the ICER to changes in particular variables, the upper and lower ICERs themselves should be interpreted with caution as a negative ICER can imply one of two directly contradictory results. Either PANO/BTZ/DEX dominates (has lower costs and greater QALYs than) LEN/DEX or is dominated by (has greater costs and lower QALYs than) LEN/DEX.

2.5.1.2. Scenario analysis

Scenario analysis were also carried out by varying input values of parameters:

1. 5% discount rate for costs and effects rather than 3.5%;
2. 5 and 10 years of time horizon used instead of 25 years;
3. Overall survival with Kaplan-Meier plus best fitting as well as Weibull methods instead of Gompertz;
4. Progression-free survival was modelled with Gompertz instead of Weibull;
5. Time to discontinuation was modelled with Kaplan-Meier curves instead of the fitted exponential survival curve;
6. Distribution of fourth line treatments a) equal to the PANORAMA-1 full trial sample and b) equal to prior IMiD population of the PANORAMA-1 trial;
7. Utility associated with LEN/DEX equal to off-treatment rather than the one used for BTZ/DEX;
8. Results of scenario analysis: various methodologies applied:

- Unadjusted Cox (full trial sample);
- MAIC (full trial sample);
- Naïve (2 to 3 prior lines of treatment);

9. Threshold analyses various HR of PFS (instead of 1.061) for LEN/DEX versus PANO/BTZ/DEX. HR of PFS was set at:
   - 0.8;
   - 0.9;
   - 1.0;
   - 1.1;
   - 1.2.

The scenario analysis assumed **SC administration** of BTZ only for the subpopulation of **2 to 3 prior lines,** using the Unadjusted Cox method (except when the scenarios with other indirect comparison methods were tested) **when the PAS is applied**. The company present a number of tables for the scenario analyses. However, as noted in the ERG report, some of the model parameters have been updated by Novartis during the clarification stage and the company did not provide the updated ICER calculations. During the clarification phase Novartis also failed to present the updated sensitivity analysis results.. In the PAS submission, Novartis, however submitted the updated findings and the ERG have checked the results of the sensitivity analyses. All scenarios analyses were re-run in the model by the ERG. The tables presented in the sensitivity analysis section of the PAS were verified by the ERG. The figures were found to be consistent with the model outputs.

The ICER is found to be sensitive to:

- Applying Kaplan-Meier plus best fitting and Weibull methods instead of Gompertz for the OS. This changed the ICER from dominant to £32,230 for the Weibull method and to £16,236 for the Kaplan-Meier plus best fitting method;
- Applying the Naïve comparison method to the population who received 2 to 3 prior lines of treatment results in an ICER of £341,896;
- Varying the HR of PFS changes the ICER from dominant to up to £79,225 per QALY gain. Lowering the HR increases the ICER. If the HR of PFS is set at 0.8 instead of 1.061 the ICER increases to £223,848. If the HR is set at 0.9 the ICER is set at £98,040, an HR of 1 results in an ICER of £24,707.The HR of 1.1 and 1.2 both result in a dominant ICER.

Varying other parameters did not change the conclusion on cost-effectiveness (ICER).

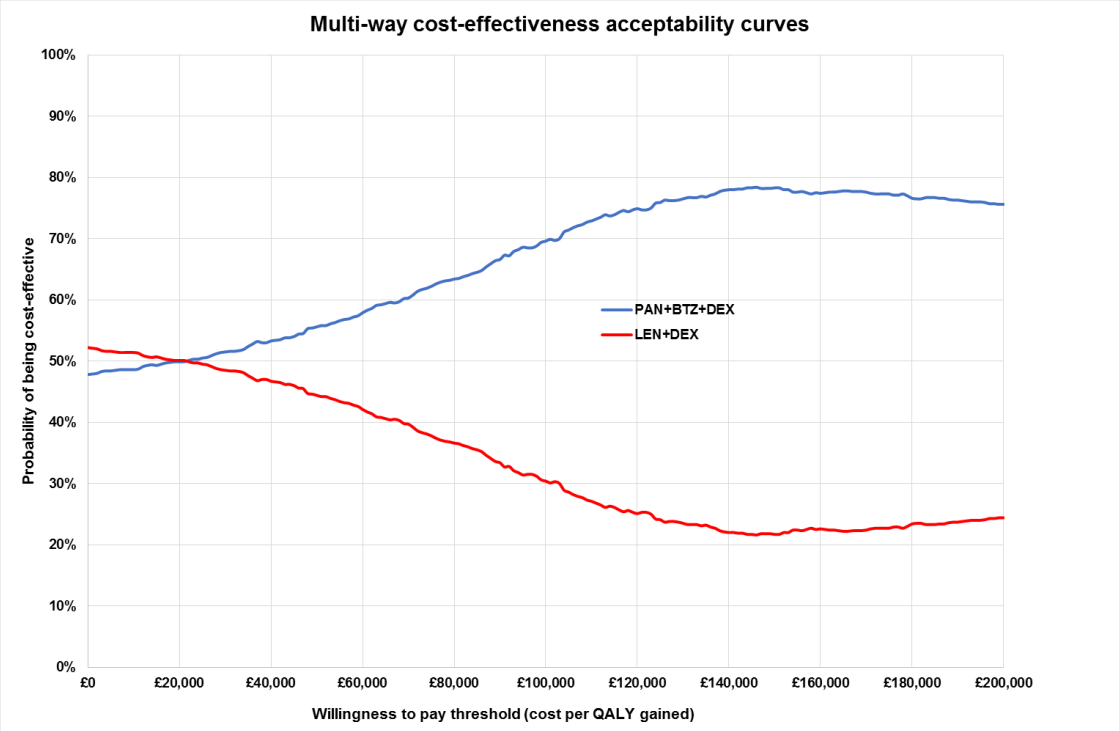
2.5.2. Probabilistic result

The PSA is summarised in the PAS submission by cost-effectiveness acceptability curves (CEACs) and a cost-effectiveness acceptability frontier (CEAF). The PSA is described as relating to the company's base case in which PANO/BTZ/DEX is dominant on the basis of the mean deterministic ICER. Given that the curves for PANO/BTZ/DEX and LEN/DEX cross at a willingness to pay (WTP) of around £30,000 per QALY, i.e. the ICER for PANO/BTZ/DEX is greater than £30,000 per QALY gained in 50% of simulations. We would expect the mean probabilistic ICER to be around £30,000 per QALY for this simulation. The CEAF shows PANO/BTZ/DEX becoming the preferred option at a WTP of a little below £20,000 per QALY.

These probabilistic results may seem surprising given that the manufacturer's mean deterministic results with the PAS and base case assumptions show PANO/BTZ/DEX generating positive QALYs and

cost savings (i.e. dominant). However, the ERG has obtained a probabilistic ICER of around £19,000 in one of a number of PSA simulation in the manufacturer's model. As noted above, the PSA tends to give a less favourable result for PANO/BTZ/DEX than the deterministic result. Figure 1 illustrates the CEACs for PANO/BTZ/DEX and LEN/DEX in this case, the underlying data showing that they cross at a WTP of close to £20,000 per QALY.

Figure 1: Illustrative CEAC based on the manufacturer's base case with PAS



3. Conclusion

The ERG have verified the manufacturer's new deterministic base case result when applying the PAS with simple discount of [redacted] %. In this case PANO/BTZ/DEX generates cost savings as well as QALY gains when compared with LEN/DEX (i.e. PANO/BTZ/DEX is dominant) for patients who have received at least two prior lines of therapy including an IMiD drug and BTZ. Given the marked improvement for PANO/BTZ/DEX from an ICER of over £[redacted] per QALY gained relative to LEN/DEX to dominating LEN/DEX in the deterministic analysis, the ERG also investigated the results of the probabilistic analysis.

The results of the probabilistic analysis differed sufficiently from those of the deterministic analysis to indicate nonlinearities in the model; where this is the case, **the probabilistic results are usually preferred to the determinist**ic. The probabilistic simulations run by the ERG using the manufacturer's model tended to give less favourable results for PANO/BTZ/DEX than the deterministic analysis (with and without PAS). While the company's deterministic analysis showed PANO/BTZ/DEX to be dominant in the base case, the company's probabilistic simulations, suggested that LEN/DEX may be the preferred therapy below a WTP of around £20,000 per QALY.

The company's submission presents a number of scenario analysis, the results of which have been verified by the ERG. However, the company's submission did not explore the impact of using the MAIC approach to estimating the relative effectiveness of LEN/DEX vs. PANO/BTZ/DEX (as captured by the model's HRs). The impact of adopting this approach, combined with the manufacturer's other base case assumptions, is to give a mean ICER for PANO/BTZ/DEX relative to LEN/DEX of £95,683 per QALY gained in the deterministic analysis.

The MAIC is the ERG's preferred method to estimating HRs in the indirect treatment comparison (as discussed in the ERG report in report to the company's original submission). Using the ERG's clinical expert preferred assumptions slightly decrease **the deterministic ICER to £92,306 for PANO/BTZ/DEX relative to LEN/DEX**. The corresponding deterministic ICER using the same preferred method and assumptions is £108,143 per QALY gained without the PAS.

Using the ERG's preferred method to estimating HRs and preferred assumption gave the probabilistic ICER of £99,880 in the simulation presented in this report. This is the ERG's preferred ICER estimate.

Compared with the impact of using MAIC rather than the Unadjusted Cox method, varying other parameters in the manufacturer's sensitivity and scenario analyses had relatively little effect on the results.