NICE National Institute for Health and Care Excellence

NICE guidance

Panobinostat for treating multiple myeloma after at least 2 previous treatments

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendations

1.1 Panobinostat in combination with bortezomib and dexamethasone is recommended, within its marketing authorisation, as an option for treating multiple myeloma, that is, for 'adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent' when the company provides panobinostat with the discount agreed in the patient access scheme.

2 The technology

2.1 Panobinostat (Farydak, Novartis Pharmaceuticals) 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 has received a marketing authorisation in combination with bortezomib and dexamethasone, for the treatment of 'adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent'.

2.2 In the PANORAMA-1 trial (comparing panobinostat plus bortezomib and dexamethasone with placebo plus bortezomib and dexamethasone), diarrhoea, thrombocytopenia, anaemia, fatigue and nausea occurred more often with panobinostat plus bortezomib and dexamethasone than with placebo plus bortezomib and dexamethasone.

2.3 Panobinostat costs £776 per 20 mg tablet. 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 cycle. Patients should have panobinostat for 8 cycles, after which it is recommended that patients showing clinical benefit continue the treatment for 4 additional cycles of 6 weeks each. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of panobinostat, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Evidence

The Appraisal Committee considered evidence submitted by Novartis and a review of this submission by the Evidence Review Group. See the Committee papers for full details of the evidence.

Clinical effectiveness

3.1 The company included 1 randomised controlled trial, PANORAMA-1, which compared panobinostat, bortezomib and dexamethasone with bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma, and who have had 1 to 3 previous treatments. The trial spanned 34 countries and 215 centres (30 of which were 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. Approximately one third (35% in the intervention group and 37% in the comparator group) of patients in the trial had relapsed and refractory multiple myeloma and approximately half had received more than 2 lines of treatment (48.8% for the intervention group and 48% for the comparator group). A subgroup of patients who had at least 2 previous lines of treatment, including 1 immunomodulatory drug (for example thalidomide) and bortezomib (n=147, 19% of the trial population), was a post hoc subgroup whereas other subgroups were pre-specified in the trial. This is the subgroup which received the marketing authorisation and will be the only group described in this section.

3.2 Treatment allocation in the trial was blinded and no crossover occurred. The trial was divided into phase 1 (24 weeks; 8 cycles of 21 days' each) and phase 2 (24 weeks; 4 cycles of 42 days' each). During phase 1, in week 1 and 2 of each cycle patients had 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 experienced clinical benefit, defined as at least no disease progression on day 1 of cycle 8 (as assessed by the modified European Group for Blood and Marrow Transplantation criteria).

3.3 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 was defined as the time from randomisation until documented disease progression, relapse from complete response or death, whichever came first. The final analysis was done 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 had a different treatment. In the PANORAMA-1 trial, patients in the subgroup having panobinostat plus bortezomib and dexamethasone (Pano-Bort-Dex) had a median progression-free survival extension of 7.8 months compared with placebo, representing a 53% reduction in the risk of progression.

3.4 The key secondary outcome was overall survival, which was defined as the time from randomisation to death from any cause. 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.

3.5 The company performed an indirect comparison for the subgroup of people who had at least 2 previous lines of treatment, including 1 immunomodulatory drug plus bortezomib, to compare Pano-Bort-Dex with bortezomib and lenalidomide. The indirect comparison included: PANORAMA-1, MM-009 and MM-010 for lenalidomide plus dexamethasone (Len-Dex); DOXIL-MMY-3001for bortezomib plus dexamethasone (Bort-Dex); and APEX for bortezomib. The company considered Len-Dex to be the only relevant comparator for the subgroup.

3.6 Three different methods were used for the indirect treatment comparison for the subgroup who had at least 2 previous therapies: naive comparison, unadjusted Cox regression and matching adjusted indirect treatment comparison.

3.7 For the matching adjusted indirect treatment comparison, patient-level data from the PANORAMA-1 trial were used for the panobinostat group whereas data from the pooled analysis of the MM-009 and MM-010 studies and a subgroup from Stadtmauer et al. (2009) were used for the Len-Dex group. Individual patient-level data from the PANORAMA-1 trial were reweighted such that the median baseline characteristics matched those reported from the MM-009 and MM-010 trials. These variables included age, sex, time since diagnosis, ECOG

score, number and type of previous treatments (immunomodulatory drugs and bortezomib) and serum beta-2 microglobulin level. The hazard ratios for progression-free survival and overall survival were 1.108 and 1.413 respectively.

3.8 Adverse events were reported for the PANORAMA-1 trial. The numbers of patients in the Pano-Bort-Dex group who needed at least 1 dose change 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 Pano-Bort-Dex group, and fatigue and pneumonia in the placebo plus bortezomib and dexamethasone group. The incidence of adverse events was much lower during phase 2, when bortezomib and dexamethasone were administered less frequently.

Cost effectiveness

3.9 The company developed 2 models – 1 for the full population in PANORAMA-1 and 1 for the subgroup who had at least 2 previous treatments including an immunomodulatory drug and bortezomib. This section relates only to the subgroup.

3.10 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 done from an NHS and personal social services perspective.

3.11 Transition probabilities for Pano-Bort-Dex were derived from post hoc patient-level data from PANORAMA-1, and included progression-free survival, treatment exposure and overall survival.

3.12 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. The time between randomisation and progression, death or censoring was considered to be the length of treatment exposure.

3.13 To determine the proportion of patients who were on or off treatment, patient-level discontinuation data from the PANORAMA-1 trial were used to estimate the risk of treatment discontinuation in a 3-week cycle. In this analysis, the length of treatment exposure for a patient was considered the time to treatment discontinuation.

3.14 For the overall survival analysis, time between randomisation and death or censoring was considered as treatment exposure. Patients were censored at the last contact date if they were lost to follow-up for survival status measurements.

3.15 Patients in the PANORAMA-1 trial completed an EORTC QLQ-C30 questionnaire, which was mapped to obtain the corresponding EQ-5D utility value. Cycle-specific as well as overall average and median utility values were estimated for the treatment arms.

3.16 No utility data were available for Len-Dex so 2 scenarios were explored. In the first, the utility value for Len-Dex was assumed to be the same as that for Bort-Dex. 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.

3.17 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-day cycle cost for lenalidomide was £3,773, which translated into a 3-weekly (21-day) cycle cost of £2,830 (taking into account the patient access scheme for lenalidomide). The cost for dexamethasone was £2.59 per 28-day cycle (£1.94 per 3-weekly cycle). The panobinostat costs included in the model are confidential because a patient access scheme has been agreed between the company and the Department of Health. The patient access scheme for bortezomib was not included in the company's analyses, because it only applies to bortezomib monotherapy in people whose multiple myeloma has relapsed for the first time after having one treatment (see NICE's

technology appraisal guidance on bortezomib monotherapy for relapsed multiple myeloma).

3.18 The company considered that the unadjusted Cox method was most appropriate to derive the relative efficacy of Pano-Bort-Dex compared with that of Len-Dex.

3.19 The company provided a number of different scenarios, which were: changes to the discount rate, how overall and progression-free survival were calculated, time to discontinuation, distribution of post-progression treatments, utility values associated with Len-Dex, how hazard ratios were generated, and threshold analyses.

ERG's critique and exploratory analyses

3.20 The ERG considered that the population in the PANORAMA-1 trial generally reflected relapsed and refractory multiple myeloma patients in the UK, although it noted that with a median age of 63 years, the trial population was younger than most UK patients. It also considered that people in the trial had bortezomib up to cycle 16, but in UK clinical practice patients do not have bortezomib beyond cycle 8, with a stopping rule at 4 cycles if no response is seen. The ERG noted that patients in the trial were administered bortezomib intravenously but that in UK clinical practice it is becoming more common to administer bortezomib subcutaneously.

3.21 The ERG considered the company's use of parametric curves fitted to the Kaplan–Meier data to be appropriate to extrapolate beyond the trial time horizon, and noted that the use of logistic regression was particularly appropriate because of the binary nature of the responses (progressed or not progressed). However, the ERG noted that the Len-Dex overall survival curve had not been compared with the underlying trial data.

3.22 The ERG also observed that the hazard ratios for progression-free survival and overall survival were calculated using 2 methods of indirect comparison: unadjusted Cox regression and matching adjusted indirect treatment comparison. For the unadjusted Cox regression, the proportional hazards assumption was not consistent with the shape of the Kaplan–Meier curves for progression-free

survival or overall survival for patients having either treatment. The ERG noted that the curves crossed, suggesting that hazard ratios were likely an invalid method of estimating relative effectiveness. The ERG therefore considered that the matching adjusted indirect treatment comparison approach was a more potentially valid method of obtaining point estimates of relative effectiveness, although it reduced the effective sample size and may have increased unobserved confounding and bias.

3.23 The ERG considered that the costs and resources used in the model were generally acceptable. 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 clinical experts also confirmed that most patients have bortezomib subcutaneously because of better tolerance.

Company's new evidence in response to consultation

3.24 In response to consultation on the appraisal consultation document, the company provided a revised economic analysis that contained all of the ERG's revisions (see sections 3.22 and 3.23). The company submitted 2 new cost-effectiveness analyses, one incorporating the following:

- Time-dependent hazard ratios derived using the matching adjusted indirect comparison method after independently fitting parametric curves to the Pano-Bort-Dex and Len-Dex data
- a comparison of Pano-Bort-Dex with Bort-Dex for patients with relapsed and/or refractory multiple myeloma who have had at least 2 prior regimens including bortezomib and an immunomodulatory agent.

  The second analysis incorporated the points above and also included an updated patient access scheme for panobinostat. This used a confidential simple discount on the list price of panobinostat and final 5 year overall survival data from the PANORAMA-1 trial (academic in confidence and cannot be presented). The patient access scheme for bortezomib was not included in the company's analyses because it only applies to bortezomib

monotherapy in people whose multiple myeloma has relapsed for the first time after having one treatment (see NICE's technology appraisal guidance on bortezomib monotherapy for relapsed multiple myeloma). Only the results from this second analysis are presented in this final appraisal document (see sections 3.25 to 3.27).

3.25 For the comparison of Pano-Bort-Dex with Len-Dex, the company's new analysis resulted in a deterministic incremental cost-effectiveness ratio (ICER) of £11,527 per quality-adjusted life year (QALY) gained and a probabilistic ICER of £11,883 per QALY gained. For Pano-Bort-Dex compared with Bort-Dex, Pano-Bort-Dex dominated (that is, was more effective and less expensive than) Bort-Dex for both the deterministic and probabilistic ICERs.

3.26 The company also provided several new scenario analyses, all of which incorporated the updated patient access scheme. For the comparison with Len-Dex, the company presented the following scenarios:

- When using a Weibull parametric curve, the ICER increased from £11,527 to £33,385 per QALY gained.
- When using the Kaplan–Meier data and extrapolating using a Gompertz model, the ICER increased from £11,527 to £17,891 per QALY gained.
- When different models were used for the progression-free survival data, the ICER decreased and was more favourable to panobinostat.
- When the company assumed no active treatment after disease progression, Pano-Bort-Dex dominated (that is, was less expensive and more effective than) Len-Dex.

3.27 The company also carried out a number of scenarios for the comparison of Pano-Bort-Dex with Bort-Dex. In all scenarios Pano-Bort-Dex dominated (that is, was less expensive and more effective than) Bort-Dex except when different approaches were used to extrapolate the overall survival data (which increased the ICERs to over £100,000 per QALY gained).

Evidence Review Group's critique of the company's

new evidence

3.28 The ERG focused its critique on both comparisons presented by the company: Pano-Bort-Dex compared with Len-Dex and Pano-Bort-Dex compared with Bort-Dex.

3.29 The ERG raised concerns about the use of the matching adjusted indirect comparison method and therefore the comparison of Pano-Bort-Dex and Len-Dex. It noted that the comparative effectiveness analysis using this method was more questionable in terms of survival outcomes, because these were likely to be affected by subsequent lines of treatment across the trials included in the comparison (PANORAMA-1 for Pano-Bort-Dex and MM-009 and MM-010 for Len-Dex), although the company had considered them to be equivalent. The ERG was concerned that the company only matched 2 baseline characteristics between the patient groups (time since diagnosis and beta-2-microglobulin levels).

3.30 The ERG also noted that in the scenario analysis assuming no treatment after disease progression, the company had only removed the subsequent costs and not the clinical effectiveness associated with these treatments. The ERG was concerned that overall survival gain for Pano-Bort-Dex and Bort-Dex was likely to be driven by differences in the subsequent treatments given after disease progression.

3.31 The ERG was unsure why the company had used a Weibull parametric curve to model overall survival when this was no better a fit than the exponential curve. The ERG considered that this should have been included in the company's sensitivity analyses.

3.32 The ERG noted that in all the company's analyses it had extrapolated the Pano-Bort-Dex and Bort-Dex curves beyond 55 cycles of treatment, which was the post-progression phase. The ERG noted that the survival curve for Pano-Bort-Dex crossed the survival curve for Bort-Dex at this point and yet the company had extrapolated until cycle 61 (using small numbers; Pano-Bort-Dex n=15 and Bort-Dex n=21), at which point it considered there was no difference in the survival of the 2 groups. The ERG noted that the company did not include a scenario where no survival difference was incorporated from cycle 55 onwards.

3.33 The ERG repeated the company's probabilistic sensitivity analyses. For Pano-Bort-Dex compared with Len-Dex, it found ICERs between £20,000 and £25,000 and so considered the true ICER to be greater than the company's ICER of £11,527 per QALY gained. For Pano-Bort-Dex compared with Bort-Dex, the ERG found that Pano-Bort-Dex dominated in all scenarios.

4 Committee discussion

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of panobinostat, having considered evidence on the nature of multiple myeloma and the value placed on the benefits of panobinostat by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical need and practice

4.1 The Committee considered the current pathway for people with multiple myeloma. It heard from the clinical experts that the pathway of treatment is heterogeneous and people could have either thalidomide or bortezomib, plus an alkylating agent (for example melphalan or chlorambucil) and a corticosteroid (for example dexamethasone), as first-line treatment as recommended in NICE's technology appraisal guidance on bortezomib and thalidomide for the first-line treatment of multiple myeloma. This may be followed by bortezomib and then lenalidomide (see NICE's technology appraisal guidance on bortezomib monotherapy for relapsed multiple myeloma and lenalidomide for the treatment of multiple myeloma in people who have received at least 2 previous therapies). The Committee also heard from the clinical experts that almost all patients have bortezomib by subcutaneous rather than intravenous administration, even though recommendations in the current British Committee for Standards in Haematology guideline for the diagnosis and management of multiple myeloma (2014) suggest either can be used. The Committee considered that treatment with an immunomodulatory agent and bortezomib was established practice in the NHS and that bortezomib was most often administered to patients subcutaneously. The Committee also heard from the clinical experts that panobinostat plus bortezomib and dexamethasone would likely fit in the treatment pathway at the same point as lenalidomide plus dexamethasone (that is, after bortezomib and dexamethasone), and so the Committee considered that lenalidomide plus dexamethasone was the most appropriate comparator to panobinostat plus bortezomib and dexamethasone in this appraisal.

4.2 The Committee heard from patient experts about the nature of multiple myeloma

and their experiences of treatment. It heard that multiple myeloma is a life-long condition that has a serious effect on quality of life. It can develop at a young age, and affects all aspects of life including education, work, self-care, and social and family life. The Committee heard from the patient experts that desired treatment outcomes are about both survival and quality of life. It also heard that people can be anxious about relapsing because few treatment options are available if they do, and that people consider a range of treatments to be important because they have different experiences with different treatments. The Committee heard from the clinical and patient experts that the multiple myeloma population is heterogeneous and has life-long disease, so there may be a place in the treatment pathway for another therapy with a different mechanism of action. The Committee also heard from the clinical and patient experts that there is a clinical need for alternative treatments for multiple myeloma in people who have had at least 2 previous treatments including an immunomodulatory agent and bortezomib. The Committee recognised the importance of having effective and tolerable treatment options for people with multiple myeloma who have had at least 2 previous treatments.

Clinical effectiveness

4.3 The Committee considered the evidence presented by the company on the clinical effectiveness of panobinostat. It noted that the main source of evidence was the PANORAMA-1 trial, which compared panobinostat plus bortezomib and dexamethasone with placebo plus bortezomib and dexamethasone in patients who had relapsed or relapsed and refractory multiple myeloma and had received 1 to 3 previous treatments (see sections 3.1 and 3.2). The Committee noted that the trial was well conducted and showed that progression-free survival was statistically significantly greater for the panobinostat plus bortezomib and dexamethasone group than for the placebo plus bortezomib and dexamethasone group. The Committee considered the generalisability of the PANORAMA-1 trial to UK clinical practice. It noted that, compared with clinical practice, the population in the trial was generally younger, a greater number of patients in the trial had a previous stem cell transplant, and bortezomib was prescribed for longer (up to 12 cycles in the trial rather than 8 used in established practice in the NHS). The Committee also noted that only a subset of the trial population matched the population for which panobinostat had received a marketing authorisation (that

is, people with relapsed and refractory multiple myeloma who have had at least 2 treatments including an immunomodulatory treatment and bortezomib). It noted that this subgroup analysis was not pre-specified in the trial. It further noted that the marketing authorisation for panobinostat was for the subgroup and not for the full population in the PANORAMA-1 trial. Nevertheless, the Committee accepted that the results from the PANORAMA-1 trial used in the post hoc subgroup analysis demonstrated that panobinostat plus bortezomib and dexamethasone was clinically more effective than bortezomib plus dexamethasone based on the PANORAMA-1 trial interim and final overall survival data. The Committee concluded that the subgroup results were relevant and generalisable to patients who have had at least 2 previous treatments in established practice in the NHS and considered that panobinostat plus bortezomib and dexamethasone was clinically effective.

4.4 The Committee noted that there were no direct head-to-head trials comparing panobinostat plus bortezomib and dexamethasone with lenalidomide plus dexamethasone and therefore an indirect comparison would be needed. The Committee considered the comparators in the indirect comparison and the indirect methods used by the company. The Committee heard from the clinical experts that comparing the lenalidomide trials MM-009 and MM-010 with the PANORAMA-1 trial was difficult because the baseline characteristics of the patients were very different. The clinical experts commented that MM-009 and MM-010 took place when fewer and less effective treatment options were available, making a comparison based on previous lines of treatment unreliable. The Committee considered the company's matching adjusted indirect comparison of panobinostat plus bortezomib and dexamethasone with lenalidomide plus dexamethasone, one of the comparators in the NICE scope and included in the company's submission (see section 3.6). It heard from the ERG that the methods used to identify both published and unpublished studies for the network meta-analysis were appropriate, and the studies were mostly well reported. The Committee understood that the company had incorporated a population into the comparison who had received 2 or 3 previous treatments but not necessarily bortezomib and an immunomodulatory drug. It heard from the company that the matched patients taken from the PANORAMA-1 trial and the MM-009 and MM-010 trials were based on baseline prognostic factors which predict survival. The company explained that it considered time since diagnosis, number of previous treatments, beta-2-microgobulin levels and International Staging System

(ISS) stage to be significant predictors of survival. The company also explained that ISS data were not reported in the 2 to 3 previous treatment subgroup analysis of the MM-009 and MM-010 trials. The Committee heard from the company that adjusting for a limited number of patient characteristics avoids smaller sample sizes, which would reduce the statistical power of the analyses. The Committee was aware that there were other baseline characteristics in both the PANORAMA-1 and MM-009 and MM-010 trials that could have been adjusted for, and that further adjustments to these baseline characteristics might have increased the robustness of the analysis. The Committee was also aware that the matching adjusted indirect comparison was done in a population who had received 2 to 3 previous treatments but not necessarily bortezomib and an immunomodulatory agent, so was not consistent with the population in the marketing authorisation for panobinostat plus bortezomib and dexamethasone. The Committee noted the limitations of the company's comparison but accepted that the hazard ratio results suggested that panobinostat plus bortezomib and dexamethasone had a similar level of clinical effectiveness to lenalidomide plus dexamethasone.

4.5 The Committee considered the adverse event profile associated with panobinostat in the PANORAMA-1 trial. It noted that diarrhoea was the most common adverse event in the trial, and was more frequent in the panobinostat plus bortezomib and dexamethasone group than in the bortezomib and dexamethasone group in treatment phases 1 and 2. It also noted that frequently observed adverse events with panobinostat included thrombocytopenia, anaemia, fatigue and nausea. The Committee noted consultee statements from a patient and carer group which highlighted patients' concerns that some of the adverse events may lead to increased hospitalisation, but it was also aware that clinical experts considered it possible to adequately manage the adverse events. The Committee was also aware that the rates of discontinuation because of adverse events and on-treatment deaths with panobinostat plus bortezomib and dexamethasone were within the ranges reported for lenalidomide plus bortezomib, but were higher than in the bortezomib plus dexamethasone group in the trial (36% compared with 20%). The Committee concluded that although there were some adverse events associated with panobinostat plus bortezomib and dexamethasone treatment, they were manageable in clinical practice.

Cost effectiveness

4.6 The Committee considered the company's new models and cost-effective analyses which were submitted as a response to the appraisal consultation document (see sections 3.24 to 3.27) and the ERG's critique (see sections 3.28 to 3.33). These concerned the main comparison of panobinostat plus bortezomib and dexamethasone compared with lenalidomide plus dexamethasone, and the additional comparison of panobinostat plus bortezomib and dexamethasone compared with bortezomib plus dexamethasone.

4.7 The Committee considered the comparison with bortezomib plus dexamethasone. It recalled that the PANORAMA-1 trial provided trial data for this comparison in the population included in the marketing authorisation for panobinostat. However, the Committee considered that this analysis was not needed for its decision-making because the company had provided a new indirect comparison (see section 4.8) with the relevant comparator (lenalidomide plus dexamethasone). The Committee therefore considered that bortezomib plus dexamethasone was not the appropriate comparator and agreed not to consider this comparison further. The Committee agreed that the new cost-effectiveness analyses provided by the company for the comparison of panobinostat plus bortezomib and dexamethasone with lenalidomide plus dexamethasone were relevant to its decision-making.

4.8 The Committee considered how the company applied time-dependent hazard ratios for progression-free survival and overall survival from the matching adjusted indirect treatment comparison in the new evidence for the comparison of panobinostat plus bortezomib and dexamethasone with lenalidomide. The Committee noted that the company had fitted curves to the data but based only on the prognostic factors that predict survival (see section 4.4). The Committee considered that this was preferable to using a single model with the caveat that the company had used a Weibull distribution for extrapolating the progression-free survival data without also exploring exponential distribution. Nevertheless, the Committee concluded that the use of time-dependent hazard ratios based on the matching adjusted indirect comparison was acceptable in its decision-making.

4.9 The Committee discussed how health-related quality of life was incorporated into

the economic model, noting that the company had measured health-related quality of life in the PANORAMA-1 trial using the EORTC QLQ-C30 questionnaire, MM-specific module and EORTC-MY20 and mapped it onto the EQ-5D to provide utility values for the pre-progression with panobinostat treatment health state. The Committee noted that EQ-5D data were not available for lenalidomide plus dexamethasone and that the company used 2 scenarios for the utility value for pre-progression patients having lenalidomide (see section 3.16), but that both of these estimates were conservative and favoured lenalidomide. The Committee noted that the utility value for pre-progression no treatment was taken from Acaster et al. and was higher than pre-progression with treatment, but considered this to be an acceptable assumption because patients in this health state would not experience adverse events (because they are assumed to have no treatment). The Committee also noted that disutilities had not been incorporated in the model. However, because health-related quality of life data were collected in the PANORAMA-1 trial, these values would have included chronic adverse events. The Committee concluded that the utility values used by the company were appropriate.

4.10 The Committee discussed the costs included in the model, particularly the administration costs of bortezomib. The Committee heard from the clinical experts that almost all patients have bortezomib by subcutaneous administration (see section 4.1) and so it concluded this to be the most appropriate bortezomib cost to be included in the model.

4.11 The Committee questioned the face validity of both the calculated quality-adjusted life year (QALY) gains and the calculated cost differences. It noted that the QALY advantage for panobinostat occurred after treatment discontinuation. It heard from the company that people in the panobinostat group of the PANORAMA-1 trial remained progression-free without treatment for a longer period than in the bortezomib comparator group. The Committee also noted that the costs in the post-progression health state were lower for panobinostat plus bortezomib and dexamethasone than for lenalidomide plus dexamethasone, even though panobinostat was an additional component to the comparator regimen. The company explained that the post-progression state analyses took into account the different percentage of people who had subsequent treatment in the PANORAMA-1 trial. The company further explained that the subsequent treatments provided in the trial were not all standard

treatments in clinical practice in the UK and therefore it adjusted the treatments to reflect clinical practice in the UK. The company highlighted that because subsequent treatment data had not been published for lenalidomide plus dexamethasone, it assumed that patients in this comparator group received the subsequent treatments in similar proportions to those reported for panobinostat plus bortezomib and dexamethasone. The Committee was aware that in its new analyses, the company had removed the costs of subsequent treatment but did not adjust the clinical effectiveness, causing a mismatch between the total costs and efficacy of panobinostat. However, the Committee heard from the company that it considered the analysis to be a conservative estimate for panobinostat because the previous treatment received in the lenalidomide trials would have been different. The Committee noted that the company's view was consistent with the clinical experts (see section 4.4). The Committee concluded that it wasn't clear which subsequent treatments and costs had been included by the company and that there was potential bias in assuming the costs of UK-specific treatments but using the efficacy of the subsequent treatments in the PANORAMA-1 trial.

4.12 The Committee considered the company's new cost-effectiveness analyses for panobinostat plus bortezomib and dexamethasone compared with lenalidomide plus dexamethasone. Considering all of the new evidence available for this comparison, which included the updated patient access scheme (see section 3.24),the Committee agreed that the ICER was likely to be no higher than £25,000 per QALY gained and therefore within the range that would normally be considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). The Committee concluded that it could, therefore, recommend panobinostat plus bortezomib and dexamethasone as a treatment option for adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior treatment regimens including bortezomib and an immunomodulatory agent.

4.13 The Committee discussed whether panobinostat could be considered innovative. It heard from the clinical and patient experts that panobinostat may provide an additional treatment option for patients because of its different mode of action to existing treatments. However, given its previous conclusion on clinical efficacy (see section 4.3 and 4.4), the Committee considered that panobinostat was not a step-change in treatment. The Committee concluded that there were no

additional gains in health-related quality of life over those already included in the QALY calculations, and that there was no need to change its conclusions on that basis.

4.14 The Committee considered whether it should take into account the consequences of the 2014 Pharmaceutical Price Regulation Scheme (PPRS), and in particular the PPRS Payment Mechanism, when appraising panobinostat. The Committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there was any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of panobinostat. It therefore concluded that the PPRS Payment Mechanism was not applicable for the consideration of the cost effectiveness of panobinostat plus bortezomib and dexamethasone.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

5.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has relapsed and/or refractory multiple myeloma and the healthcare professional responsible for their care thinks that panobinostat is the right treatment, it should be available for use, in line with NICE's recommendations.

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