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Single Technology Appraisal (STA) of lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy with bortezomib (partial review of TA171)

Celgene submission of evidence

8 November 2013

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List of abbreviations

AFT	Accelerated failure time
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AE	Adverse event
Ben	Bendamustine
Bev	Bevacizumab
Bor	Bortezomib
BSC	Best supportive care
CDF	Cancer Drug Fund
(n)CR	(near)Complete response
CSR	Case study reports
Cyclo	Cyclophosphamide
Dex	Dexamethasone
Dox	Doxorubicin
DOR	Duration of response
EBMT	European Society for Blood and Marrow Transplantation
ECOG (PS)	Eastern Cooperative Oncology Group (performance status)
EHA	European Hematology Association
EMA	European Medicines Agency
Eto	Etoposide
FDA	Food and Drug Administration
G-CSF	Granulocyte-colony stimulating factor
HCHS	Hospital and Community Health Services
HDT	High-dose therapy
HMRN	Haematological Malignancy Research Network
HR	Hazard ration
ICER	Incremental cost-effectiveness ratio
IDMC	Independent Data Monitoring Committee
IFR	Individual funding requests
IMiDs	Immunomodulatory drugs
IMWG,	International Myeloma Working Group
ISS	International Staging System
ITT	Intention to treat
IVRS	Integrated voice-response system
Len	Lenalidomide
MDS	Myelodysplastic syndromes
MHRA	Medicines and Healthcare products Regulatory Agency
MM	Multiple myeloma
MP	Melphalan and prednisone (prednisolone)
MTD	Maximum tolerated dose
N/A	Not applicable
NCI(-CTC)	National Cancer Institute (common toxicity criteria)
NE	Not evaluated
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NK	Natural killer (cells)
NOS	Not otherwise specified
NR	Not reported
OS	Overall survival
ORR	Overall response rate
PD	Progressive disease
PFS	Progression-free survival

PH	Proportional hazard
POM	Pomalidomide
PLD	Pegylated liposomal doxorubicin
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
RCT	Randomised controlled trial
RI	Renal impairment
RR	Remission response
rrMM	Relapsed or refractory multiple myeloma
SAE	Serious adverse event
SCT	Stem cell transplant
SD	Stable disease
SMC	Scottish Medicines Consortium
SPC	Summary of product characteristics
TFI	Treatment-free interval
Thal	Thalidomide
TTF	Time to treatment failure
TTP	Time to progression
QALY	Quality-adjusted life year
VAD	Vincristine, adriamycin (doxorubicin) and dexamethasone
VIF	Variance inflation factor
VGPR	Very good partial response

Executive summary

Multiple myeloma is a haematological malignancy associated with a range of debilitating symptoms, and it continues to be incurable and relapsing in nature with a 5-year relative survival rate of 37%. The main aims of treatment are to prolong survival and maintain a good quality of life by controlling the disease and associated symptoms.

The UK annual incidence of multiple myeloma is 7.5 per 100,000 population, with the rate increasing with age. The primary management of individual patients is based on their fitness for chemotherapy and stem cell transplantation, which is determined by factors including their age, co-morbidities and performance status. It is estimated that high-dose chemotherapy with stem cell transplantation is inappropriate for 86% of patients.

Initial treatment for these patients consists of either thalidomide-based or bortezomib-based regimens as per the NICE TA228. Following first relapse, patients may then be considered for second-line treatment with bortezomib as per the NICE TA129. However, with the evolution of the treatment pathway and in particular the increasing use of bortezomib first line (since the publication of TA228), lenalidomide now represents an important additional treatment option for patients at first relapse. Lenalidomide is an oral immunomodulating agent with anti-neoplastic, anti-angiogenic, pro-erythropoietic and immunomodulatory properties, which was granted a marketing authorisation for treatment of multiple myeloma after 1 prior therapy in 2007. The use of lenalidomide is mostly limited to patients after 2 prior therapies (NICE TA171). However, some patients are currently successfully treated with lenalidomide after 1 prior therapy, made available by the Cancer Drugs Fund (CDF).

The efficacy of lenalidomide has been demonstrated in the MM-009 and MM-010 phase III randomised clinical trials (RCTs). A subset analysis of patients who had 1 prior therapy demonstrated an overall response rate (ORR) of 66.9%, a time to progression (TTP) of 17.1 months and progression-free

survival (PFS) of 14.1 months. The median overall survival (OS) was 42.0 months. This analysis also demonstrated that comparative treatment outcomes with lenalidomide are better when used earlier on in the pathway. Further pooled analysis provided evidence that the efficacy of lenalidomide is consistent regardless of prior therapy. Response for Len/Dex used subsequent to first-line bortezomib demonstrated a higher response (73% vs 44%) when used at second line compared to later lines of therapy.

In the treatment setting that is being appraised here, following first relapse, there is no established treatment standard, even though available information indicates that retreatment with bortezomib is fairly common. The available evidence on efficacy of treatments currently employed is of poor quality, as highlighted by a systematic literature review. Most of the identified studies were not RCTs, but were single arm, mostly observational in nature, with very few patients and limited published data. From the sources that were obtained, median PFS estimates ranged from 5.1 to 9.6 months for bortezomib; evidence for bendamustine reported only one estimate, a median of 9.3 months. An OS of 20.4 to 24.0 months was reported for bortezomib, compared to 12.4 months for bendamustine.

The cost-effectiveness of lenalidomide was determined using a Markov model developed in Microsoft® Excel. Survival was partitioned into three health states: pre-progression (on treatment), pre-progression (off treatment) and post-progression. Transition probabilities were determined for OS, PFS and time to treatment failure (TTF) curves, derived from MM-010 clinical study data. This approach was used to estimate lifetime outcomes and costs associated with patients with multiple myeloma following prior treatment with bortezomib. Life years and quality-adjusted life years (QALYs) are the primary clinical model outcomes. Cost outcomes include the cost of therapy and subsequent therapies, medical resource use and adverse event management.

The cost-effectiveness model indicates that, over a lifetime horizon, patients receiving lenalidomide plus dexamethasone (Len/Dex) following one prior treatment (with bortezomib) will experience an additional 1.31 years of pre-progression survival compared to bortezomib retreatment (Table 1). The

model estimates that lenalidomide will lead to an OS gain of 0.71 years, resulting in a QALY gain of 0.53. Discounted incremental costs associated with lenalidomide are £7,682, leading to an ICER of £14,535. Extensive sensitivity analyses performed to assess parameter and structural uncertainty indicated that the model results were sensitive to estimates of bortezomib comparative efficacy (ICERs dominant to £43,331), OS parameters and TTF parameters. Probabilistic sensitivity analysis (PSA) indicated a 73% chance of cost effectiveness at a willingness-to-pay threshold of £30,000 per QALY.

Table 1: Base-case cost-effectiveness results

Model result	Lenalidomide	Bortezomib	Incremental
Technology acquisition cost	£104,211	£47,085	£57,126
Other costs	£17,211	£66,654	-£49,444
Total costs	£121,422	£113,740	£7,682
Pre-progression LYG	2.48	1.18	1.31
Total LYG	5.74	5.03	0.71
QALYs	3.24	2.89	0.53
ICER	£14,535		

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio.
QALYs and Costs are presented with a 3.5% discount rate. LYG are undiscounted.

Given the current multiple myeloma treatment pathway it is estimated that just over 250 patients, contingent on the proportion being treated initially with bortezomib, will progress to second-line treatment each year. Patients not treated with lenalidomide at second line will invariably be treated with lenalidomide at third line, as per TA171. Enabling access to this specific cohort of patients is estimated to be initially cost saving to the NHS, while also improving patient outcomes. Based upon estimated current lenalidomide use, a budget saving of approximately £4,000 per 100,000 population in Year 1 is predicted, increasing to £7,000 per 100,000 population in Year 5.

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Name: Lenalidomide (Revlimid®).

Pharmacotherapeutic group: Immunomodulating agent.

ATC code: L04 AX04.

1.2 What is the principal mechanism of action of the technology?

Lenalidomide (Revlimid®) is an immunomodulating agent. It belongs to a class of agents referred to as immunomodulatory derivatives, and is a structural derivative of thalidomide.[1]

Lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including multiple myeloma plasma tumour cells), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.[1]

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Lenalidomide was granted European Medicines Agency (EMA) marketing authorisation for multiple myeloma on 14 June 2007.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

The EPAR notes that treatment with lenalidomide must not be started if the absolute neutrophil count (ANC) is < 1.0 x 10^9 /L, and/or platelet count is < 75 x 10^9 /L or, dependent on bone marrow infiltration by plasma cells, platelet count is < 30 x 10^9 /L.[2]

Lenalidomide is structurally related to thalidomide, a known human teratogenic substance that causes severe life-threatening birth defects. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide cannot be ruled out in humans and for this reason a risk minimisation plan was mandated and approved by the EMA and Medicines and Healthcare products Regulatory Agency (MHRA) during the licensing process to ensure that there is no foetal exposure to lenalidomide. See section 1.12.

In addition, Celgene must provide a letter and educational kits for healthcare professionals, and brochures for patients, explaining the fact that lenalidomide is expected to be harmful to the unborn child and detailing the steps that need to be taken for the medicine to be used safely. It will also supply cards for patients to ensure that all appropriate safety measures have been taken by each patient.

To monitor for potential haematological toxicity, patients are required to undergo routine blood tests, please see section 1.13.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Lenalidomide has a UK marketing authorisation for two indications:

- in combination with dexamethasone for the treatment of multiple myeloma, in adults who have received at least one prior therapy
- for treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

None

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Lenalidomide was launched in the UK on 25 June 2007. Although the licensed indication is for treatment following one prior therapy, the NICE recommendation in June 2009 restricted use to the treatment of patients who have received two or more prior therapies (TA 171) (see section 2.4).[3] However, since then lenalidomide has been prescribed for eligible patients after one prior therapy through Individual funding requests (IFR). More recently, lenalidomide was approved for funding through the Cancer Drugs Fund (CDF) as a second-line treatment.[4]

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

In addition to the EU states, lenalidomide is approved in a total of 44 countries; see appendix A for the full details of countries and indications.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Celgene intends to submit to the Scottish Medicines Consortium (SMC) in December 2013 for the same population being evaluated in this submission.

Lenalidomide is currently under appraisal by NICE in the indication of MDS (treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate), the anticipated publication date is quarter 1 2014. SMC is assessing lenalidomide in the same indication, with advice expected 10 March 2014.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 2: Unit costs of technology being appraised

Pharmaceutical formulation	Hard capsule White capsules marked “REV 25mg” Pale blue/white capsules marked “REV 15mg” Blue-green/pale yellow capsules marked “REV 10mg” White capsules marked “REV 5mg”
Acquisition cost (excluding VAT)	Cost per 21-tablet pack shown 25mg: £4,368 15mg: £3,969 10mg: £3,780 5mg: £3,570
Method of administration	Oral
Doses	25mg, 15mg, 10mg, 5mg
Dosing frequency	Daily for 21 days in a 28-day cycle
Average length of a course of treatment	The median time on treatment in the second-line setting from the clinical trials was 12.5 months (0.3-24.1)[5]
Average cost of a course of treatment	£3,773 per cycle for a mean of 28.1 cycles (see section 7.5)

Anticipated average interval between courses of treatments	Treatment is continuous until progression.
Anticipated number of repeat courses of treatments	Treatment with lenalidomide is continuous until progression.
Dose adjustments	Dosing is continued or modified based upon clinical and laboratory findings. Please see SPC section 4.2 for more details.[1]
SPC, summary of product characteristics.	

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

Due to the structural similarities with thalidomide (a known human teratogen), lenalidomide is contraindicated in women of child-bearing potential, or male partners of women of child-bearing potential, unless appropriate contraceptive measures and pregnancy testing are carried out. Women of child-bearing potential should have 2 negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to commencing treatment.

A medically supervised pregnancy test should be repeated every 4 weeks, including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.[1]

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

To monitor for potential haematological toxicity, patients are required to undergo routine blood tests to assess full blood counts weekly for the first 8 weeks of therapy, and monthly thereafter.

A letter was issued to health care professionals on the 10th June 2013 regarding the safety of lenalidomide for the treatment of MDS associated with an isolated deletion 5q cytogenetic abnormality. This letter highlighted an increase in risk of progression to acute myeloid leukemia in patients who are transfusion dependant and had complex cytogenetics at baseline compared with patients who had an isolated Del (5q) abnormality. This increased risk does not apply to the indication being appraised here.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

As per the marketing authorisation granted, lenalidomide is indicated in combination with dexamethasone for the population being appraised by NICE.

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

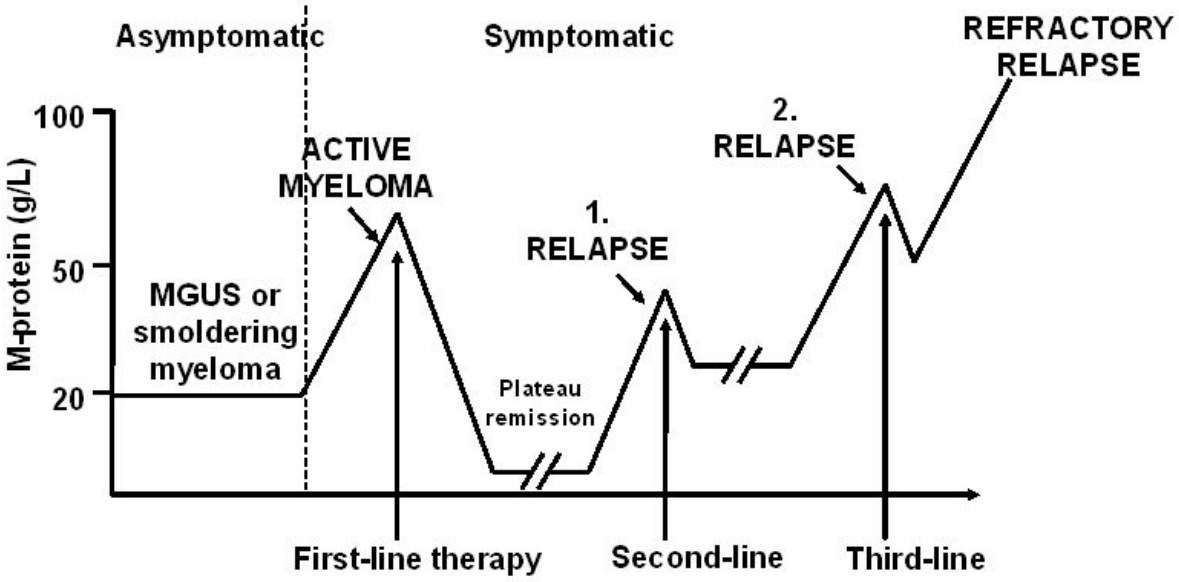
Multiple myeloma is a haematological malignancy that arises from the monoclonal expansion of plasma cells in the bone marrow.[6] Patients with multiple myeloma suffer from a range of debilitating symptoms, including skeletal destruction, which arises from activation of osteoclasts by multiple myeloma cells – leading to painful lytic bone lesions, pathological fractures and hypercalcaemia. Secretion of M-proteins by plasma cells results in renal insufficiency, and patients are also more susceptible to infection, due to a compromised B-cell lineage.[6-8]

While treatment can result in remission, the main aims of therapy are to prolong survival and maintain a good quality of life by controlling the disease and relieving symptoms.[8]

The prognostic outlook is one where patients will relapse after initial treatment, or discontinue therapy due to adverse events or toxicity, for example peripheral neuropathy. The disease also becomes refractory to

current treatments.[8] Figure 1 shows the relapsing nature of the disease. Section 2.4 provides additional detail on the life expectancy of patients with multiple myeloma.

Figure 1: Disease progression in multiple myeloma



Source: Adapted from Hajek R. Multiple Myeloma - A Quick Reflection on the Fast Progress. 2013[9]

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

Table 3 shows the total incidence of multiple myeloma in England and Wales, which is 2,368 patients. This figure was obtained using the methodology in the NICE costing template for bortezomib and thalidomide for the first-line treatment of multiple myeloma.[10] The total male and female populations aged over 20 years for each country and the respective gender-specific multiple myeloma incidence rates are used.

Table 3: Incidence of multiple myeloma in England and Wales

Item	Estimate – England	Estimate – Wales	Source
Male population (aged 20+)	18,996,481	1,096,889	NHS Information Centre for Health and Social Care (2010)[11]
Female population (aged 20+)	20,223,021	1,188,486	
Myeloma incidence (per 100,000) – Males	7.1	7.1	Cancer Research UK (2009)[12]
Myeloma incidence (per 100,000) – Females	4.4	4.1	
Total myeloma incidence	1,430	939	Calculation

The NICE costing template methodology was replicated.[10] As such, high-dose chemotherapy with stem cell transplantation is assumed to be inappropriate for 86.4% of newly-diagnosed patients, i.e. 2,047 patients, in England and Wales. Of which, 307 (15%) are unable to tolerate or are contraindicated to thalidomide. These patients therefore receive bortezomib as first-line treatment.

The proportion of patients surviving at the mean time to progression (TTP) following bortezomib, melphalan and prednisolone (1.04 years) in TA228 was estimated to be 86.5%.[13, 14] This means 266 patients are expected to progress to second-line treatment and therefore be covered in the marketing authorisation of lenalidomide for multiple myeloma.

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

According to Cancer Research UK, about 70% of people diagnosed with myeloma in the UK live for at least 1 year after diagnosis. About 37% live for at least 5 years and it is estimated that between 15% and 19% of people will live for at least 10 years.[15]

Life expectancy for multiple myeloma is usually predicted based upon the stage of the cancer. The stages are determined by the serum albumin and serum beta-2 microglobulin levels.[16] According to this system:

- At Stage I, i.e. albumin ≥ 3.5 & beta-2 microglobulin ≤3.5, the median survival is 62 months.
- At Stage II, Multiple Myeloma (beta-2 microglobulin levels are 3.5 to 5.5) it is 44 months.
- For patients with Stage III disease, who show a beta-2 microglobulin level of more than 5.5, the median survival rate reduces to 29 months.

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

NICE appraisal TA228 (July 2011 recommends thalidomide or bortezomib for the first-line treatment of multiple myeloma)[14]:

- "Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate."
- "Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if:
  - high-dose chemotherapy with stem cell transplantation is considered inappropriate; and
  - the person is unable to tolerate or has contraindications to thalidomide."

NICE recommended thalidomide as first-line treatment because it demonstrated cost and clinical effectiveness compared with alternative treatments.

NICE has previously assessed lenalidomide within its licensed indication for multiple myeloma and in June 2009 recommended it as an option for the treatment of patients who have received two or more prior therapies.[3] The recommendation was conditional on a patient access scheme.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

The submission as outlined in the decision problem is in line with the current clinical pathway; patients with multiple myeloma will only be treated with bortezomib if they are contraindicated or unable to tolerate thalidomide. Therefore treatment with lenalidomide for patients who have already received bortezomib therapy and are not suitable for retreatment is a logical step as thalidomide will already have been considered or already used as a treatment option for these patients. The EPAR noted that lenalidomide was effective for patients previously treated with either thalidomide or bortezomib (see section 1.4).

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

In TA129, NICE recommended bortezomib as an option for the treatment of progressive multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation.[17] Subsequently, TA228 recommended bortezomib in combination with an alkylating agent and a corticosteroid as an option for the first-line treatment of multiple myeloma if high-dose chemotherapy with stem cell transplantation was considered inappropriate and the person is unable to tolerate or has contraindications to thalidomide.[14]

As noted in TA228, a range of different agents are used to manage patients following relapse.[14] The British Society for Haematology guidelines for the diagnosis and management of multiple myeloma, recommend a number of options for the treatment of relapsed patients.[8]

The guidelines state that the most appropriate management must be determined on an individual basis depending on the timing of relapse, age, prior therapy, bone marrow function, co-morbidities and patient preference. In NHS England retreatment with bortezomib and/or bendamustine is commonly used in this patient population via the CDF.[4]

2.7 Please identify the main comparator(s) and justify their selection.

Bortezomib has recently received a label change for the retreatment of adult patients with multiple myeloma who have previously responded to treatment with the same medicine.[18] The main comparators for this review, based on clinical practice, include bortezomib and bendamustine. Thalidomide is excluded as patients initially treated with bortezomib will either have contraindications or be unable to tolerate it.

Information published by NHS England on the number of prescriptions related to the CDF provides an indication of the relevance of the main comparators in this submission; retreatment with bortezomib is relatively common with the CDF reporting notifications of retreatment of those patients who have previously received it and had a good response.[4]

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

The main adverse events associated with treatment with lenalidomide are neutropenia, anaemia and thrombocytopenia. The Summary of Product Characteristics (SPC) recommends dose reductions and interruptions for these events. In case of neutropenia, the physician should consider the use of growth factors in patient management. [1]

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Drug acquisition costs are obtained from British National Formulary (BNF), with the exception of dexamethasone (eMit 2013).[19, 20]

Lenalidomide is administered orally. This may require one administration appointment, but otherwise the administration burden in terms of resource use will be small. Other treatments, such as bortezomib require an administration appointment. The cost of administration and travel to administration appointments is informed by NHS reference costs 2011-12.[21]

Monitoring visits are likely to be performed by a haematologist. Lenalidomide requires patients to be monitoring weekly for the first 8 weeks of treatment and monthly thereafter. The cost of a haematologist appointment is obtained from NHS reference costs 2011-12.[21] The frequency of tests, including full blood counts, biochemistry tests, protein electrophoresis, immunoglobulin and urinary light chain excretions, is informed by a previous NICE appraisal in multiple myeloma (TA171).[3] Test costs are informed by a recent multiple technology appraisal in multiple myeloma (TA228).[22]

Terminal care is also likely to be required by some multiple myeloma patients and is informed by the King's Fund (2008).[23]

The treatment of multiple myeloma adverse events may occur in an inpatient, day case, outpatient, primary care or community care setting. This is informed by NICE submission in multiple myeloma (TA171).[3] The costs of treatment are obtained from NHS reference costs 2011-12.[21]

Resource costs are uplifted using inflation indices from the Personal Social Services Research Unit (PSSRU) where necessary.[24]

2.10 Does the technology require additional infrastructure to be put in place?

No additional infrastructure is required to treat patients in this indication. Lenalidomide is an oral therapy and therefore can be self-administered at home, with only outpatient consultations during the course of treatment. This can be of immense help to patients who have mobility problems.

3 Equality

3.1 Identification of equality issues

3.1.1 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 provide us with any evidence that would enable the Committee to identify and consider such impacts.

The application does not take into account any specific aspects related to equality as it is not anticipated that any recommendation would impact any specific group other than those within the licensed indication.

3.1.2 How has the analysis addressed these issues?

Not applicable

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a ‘step-change’ in the management of the condition.

Not applicable

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

Lenalidomide is an oral therapy and therefore can be self-administered at home, with only outpatient consultations during the course of treatment. This can be of immense help to patients who have mobility problems. However this benefit is unlikely to be reflected in the standard quality-adjusted life year (QALY) measure, particularly as the available literature for utilities in multiple myeloma is limited to health states dependent upon progression status rather than therapy received.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

A wide range of studies have confirmed that the majority of patients prefer oral to IV chemotherapy.[25-31] Questionnaire-based studies have also demonstrated a preference for home-based rather than hospital-/clinic based therapy. Oral agents offer patients a more convenient treatment option that can be administered at home, providing patients with a greater sense of control over their therapy and less interruption of their daily activities. Oral agents also avoid the medical complications and psychological distress associated with venous access and associated risks of hospital acquired infections.
This is likely to be of relevance in the population being considered who tend to be elderly and may be more prone to mobility issues and at greater risk of skeletal fractures than the general population.

5 Statement of the decision problem

Table 4: Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with multiple myeloma for whom thalidomide is contraindicated and whose disease has progressed after at least 1 prior treatment with bortezomib.	As defined in the final scope.	N/A
Intervention	Lenalidomide in combination with dexamethasone.	As defined in the final scope.	N/A
Comparator(s)	Bortezomib monotherapy and bortezomib in combination with high-dose dexamethasone Chemotherapy including regimens based on melphalan, vincristine, cyclophosphamide and doxorubicin Bendamustine	All comparators as defined in the final scope will be addressed in the submission, where evidence exists. For clarity treatment with bortezomib is referred to throughout this submission as bortezomib retreatment as in this patient population all patients will have previously received bortezomib.	N/A
Outcomes	The outcome measures to be considered include: • PFS • OS • response rates • time to next treatment • adverse effects of treatment • HRQL	All outcomes measures, excluding time to next treatment, will be addressed in the submission.	Time to next treatment was not a reported outcome in the RCTs presented in this submission.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be	The submission will provide an estimate of cost-effectiveness	N/A

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	expressed in terms of incremental cost per QALY. 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.	using the QALY as an output. The time horizon for estimating clinical and cost effectiveness will be appropriate for the indication and the population and in line with the reference case requirements. The costs will be considered from the perspective of the NHS and Personal Social Services. The costs will be presented excluding any patient access schemes for either the intervention or the comparators.	
Subgroups to be considered	None noted.	N/A	N/A
Special considerations, including issues related to equity or equality	None noted.	N/A	N/A
HRQL, health-related quality of life; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year.			

Section B – Clinical and cost effectiveness

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s).		

6 Clinical evidence

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be

provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

A systematic review was conducted in August 2013 to identify clinical studies for multiple myeloma patients treated with lenalidomide in combination with dexamethasone (Len/Dex) following initial treatment with bortezomib, as stated in the remit of the scope.

Results from previous systematic searches of Len/Dex therapy and potential comparators in relapsed or refractory multiple myeloma were updated and combined with results of systematic searches of Len/Dex therapy and specific comparators named in the decision problem in multiple myeloma.

In order to ensure the published literature was comprehensively reviewed, a wide range of databases was searched. These included: Medline, Embase, Cochrane Library, NHS EED, HTA database, DARE and CINAHL. In addition, 2011-2013 subject-specific conference proceedings of the American Society of Hematology (ASH), the American Society of Clinical Oncology (ASCO) and the European Hematology Association (EHA) were searched. Reference lists of previous systematic reviews/meta-analyses and clinical guidelines identified were hand-searched to highlight any further relevant studies.

Within the search strategy, the defined study population is wider than the one specified in the scope, as the objective was to include all potential studies, especially relevant as the search term second-line therapy was not a valid term.

Details of the search strategy used are provided in section 10.2, appendix 2.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

All studies were screened manually and included if they met all of the inclusion criteria and none of the exclusion criteria. Eligibility criteria applied are listed in Table 5.

Table 5: Eligibility criteria used in clinical search strategy

Inclusion criteria	Exclusion criteria
Population • Adult patients with rrMM with ≥1 prior treatment with bortezomib *Intervention* • Lenalidomide / dexamethasone *Comparators* • Bortezomib monotherapy • Bortezomib / high-dose dexamethasone • Melphalan, vincristine, cyclophosphamide or doxorubicin based regimens • Bendamustine *Outcomes* • Survival (OS or PFS) • Response (overall response rate, best response) • Time to next treatment • Time to progression • Safety (adverse effects of treatment) • HRQL *Study design* • RCTs • Prospective non-RCTs or observational studies of ≥5 patients *Restrictions* • Language = English	*Population* • Newly diagnosed multiple myeloma or treatment-naïve patients • Studies that investigated both newly-diagnosed and rrMM, but did not segregated the results • Studies on children and other blood cancer • Studies in which patients had no prior bortezomib *Intervention* • Lenalidomide monotherapy • Lenalidomide / any other intervention *Comparators* • Any other mono- or combination-chemotherapy • Stem cell transplantation
HRQL, health-related quality of life; OS, overall survival; PFS progression-free survival; RCT, randomised controlled trial; rrMM, refractory multiple myeloma.	

Date restriction (2011-2013) was applied only to conference proceedings and systematic review/meta-analysis in order to reflect current information on the interventions and disease area of interest to the systematic review.

Subgroup analyses were included if the analyses were based on the following:

- Elderly patient
- Patients with renal impairment (RI)
- Prior treatment analysis (primary bortezomib)
- Number of previous lines of therapy

- Long-term treatment use versus discontinuation
- Performance status
- Disease and patient characteristics

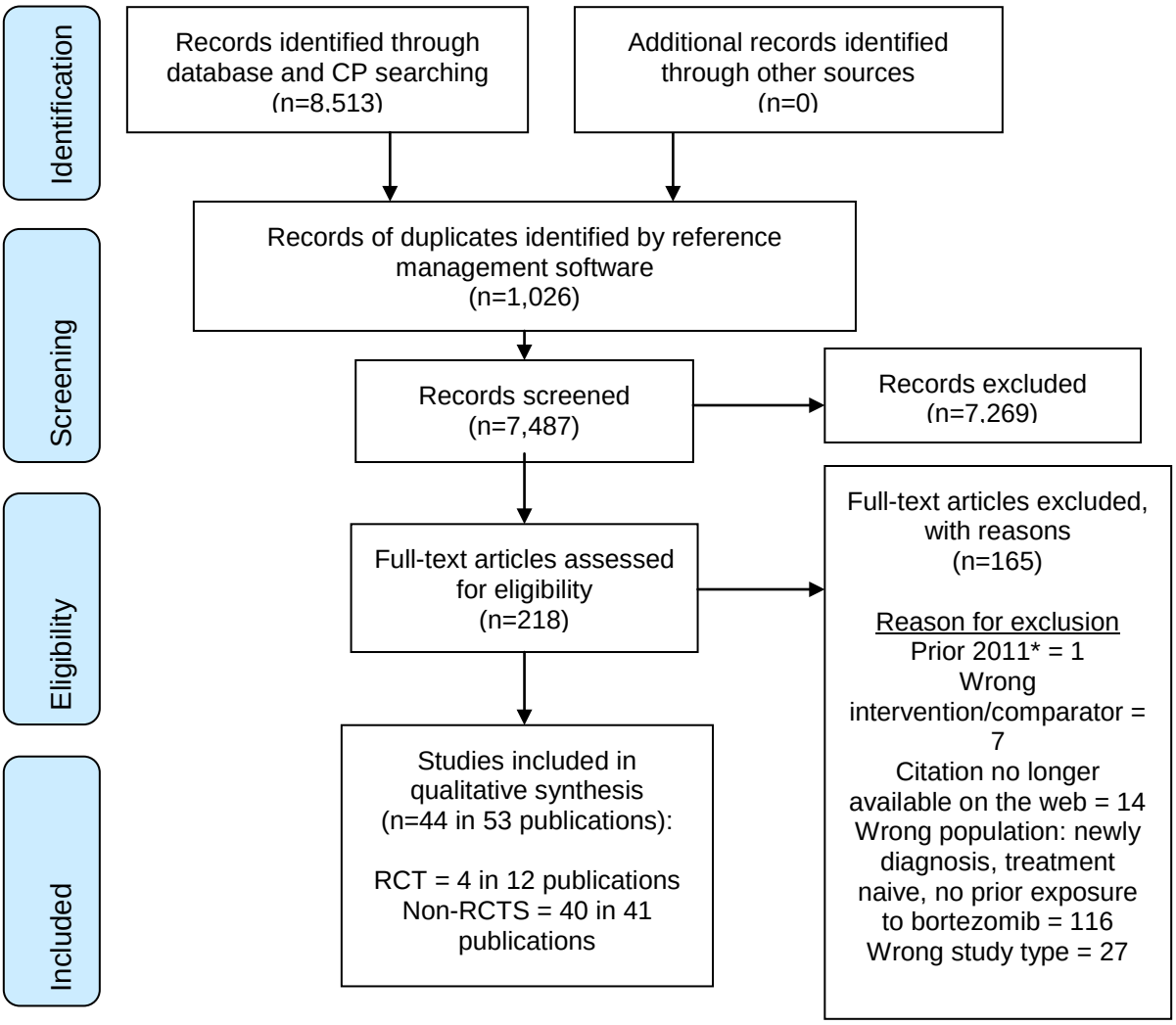
6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

Previous systematic searches of Len/Dex therapy and potential comparators in relapsed or refractory multiple myeloma, conducted in March 2013 identified 2,802 citations. 112 additional citations were identified in the update of these systematic searches, conducted in August 2013. Systematic searches of Len/Dex therapy and specific comparators in multiple myeloma, also conducted in August 2013, identified an additional 5,599 potentially relevant citations.

When combined, a total of 8,513 citations were identified from electronic database and conference proceeding searches. After removal of duplicates identified by reference management software, 7,487 citations remained and 218 citations selected for further assessment at level 2.

In total, 44 studies in 53 publications met the eligibility of the systematic review. Figure 2 summarises the study selection.

Figure 2: Flow diagram



CP, conference proceedings.
*Only systematic reviews or meta- analyses were excluded for this reason.

6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

The systematic review identified four randomised controlled trials (RCTs). In addition, six subgroup and two update analyses for two of these RCTs were identified. Details of the secondary publications are provided in Table 6.

Table 6: Relevant secondary publications

Author, year (reference)	Intervention	Comparator	Population	Publication type	Link to RCT
Dimopoulos 2009[32]	Len/Dex	Placebo/Dex	rrMM patients with ≥1 prior anti-myeloma therapy	Full paper	Updated pooled analysis of MM-009 and MM-010
Chanan-Khan 2012[33]	Len/Dex	Placebo/Dex	Elderly patients with rrMM and ≥1 prior anti-myeloma therapy	Full paper	Sub-group analysis of MM-009 and MM-010
Dimopoulos 2010a[34]	Len/Dex	_	rrMM patients with impaired renal failure and ≥1 prior anti-myeloma therapy	Full paper	Sub-group analysis of MM-009 and MM-010
Harousseau 2010[35]	Len/Dex	_	rrMM patients with ≥1 prior anti-myeloma therapy who achieved a CR or VGPR as best response compared with those who achieved a PR	Full paper	Sub-group analysis of MM-009 and MM-010
San-Miguel 2011[36]	Len/Dex	_	rrMM patients with ≥1 prior anti-myeloma therapy who achieved ≥PR	Full paper	Sub-group analysis of MM-009 and MM-010
Stadtmauer 2009[5]	Len/Dex	_	rrMM patients who had ≥1 prior lines of therapy	Full paper	Sub-group analysis of MM-009 and MM-010
Wang 2008 [37]	Len/Dex	Placebo/Dex	rrMM patients with ≥1 prior anti-myeloma therapy regardless of prior exposure to thalidomide	Full paper	Sub-group analysis of MM-009 and MM-010
Dimopoulos 2011[38]	Len/Dex	_	rrMM patients with ≥1 prior anti-myeloma therapy	Abstract	Long-term update analysis of Len/Dex of MM-009and MM-010

CR, complete response; Dex, dexamethasone; Len, lenalidomide; PR, partial response; RCT, randomised controlled trial; rrMM, relapsed or refractory multiple myeloma; VGPR, very good partial response.

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group.

Three of the RCTs examined the efficacy of Len/Dex (Richardson et al, 2006, MM-009, MM-010), while the fourth RCT examined the efficacy of bortezomib treatment (AMBER). Details of the four RCTs are shown in Table 7.

Table 7: Relevant primary publications

Author, year (reference)	Intervention	Comparator	Population	Publication type
Richardson 2006[39]	Len 30mg/ once daily/Dex	Len 15mg/ twice daily/Dex	rrMM patients with ≥1 prior anti-myeloma therapy (at least one prior chemotherapy)	Full paper
MM-010[40]	Len/Dex	Placebo/Dex	rrMM patients with ≥1 prior anti-myeloma therapy	Full paper
MM-009[41]	Len/Dex	Placebo/Dex	rrMM patients with ≥1 prior anti-myeloma therapy	Full paper
AMBER[42]	Bor/Placebo	Bor/Bev	rrMM patients with ≥1 prior anti-myeloma therapy	Full paper
Bev, bevacizumab; Bor, bortezomib; Dex, dexamethasone; Len, lenalidomide; rrMM, relapsed or refractory multiple myeloma.				

The systematic review did not identify any RCTs on the other comparators: bendamustine, bortezomib plus high-dose dexamethasone or chemotherapy including regimens based on melphalan, vincristine, cyclophosphamide and doxorubicin.

In addition to those papers identified in Table 6 and Table 7. Celgene provided two additional items:

- A paper by Mateos et al, *Bortezomib Plus Melphalan and Prednisone Compared With Melphalan and Prednisone in Previously Untreated Multiple Myeloma*: *Updated Follow-Up and Impact of Subsequent Therapy in the Phase III VISTA Trial,* that also presents responses in second and third line treatment with lenalidomide; and [43]
- An additional poster presented by Dimopoulos et al, *Consistency of LEN Plus DEX Efficacy Across Prior Treatments in Relapsed or Refractory Multiple Myeloma (MM).*[44]

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

None of the identified RCTs directly compare the intervention with the appropriate comparators. Of the four RCTs identified for the systematic review, MM-009 and MM-010 actively compared Len/Dex to placebo/Dex. While Richardson et al (2006) compared two doses of lenalidomide treatment in combination with dexamethasone: Len 30mg/Dex versus Len 15mg/Dex.

In the AMBER trial, bortezomib in combination with bevacizumab was compared with single-agent bortezomib.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

The Richardson et al paper is not discussed in further detail within the main body of the submission because it is a phase II dose-comparison study that has been superseded by the two phase III studies MM-009 and MM-010, which are of relevant doses in the correct patient population.

The AMBER study is also excluded. Although it is the only RCT for the comparators in the decision problem identified during the systematic review,

the proportion of patients who had received bortezomib as second-line treatment was low (19%) and the study did not report outcomes for this population. Due to the low retreatment rate in this trial, it has limited informative value for modelling purposes leading to the use of non-RCT trials, see section 6.8.1. Additionally, as the paper compared monotherapy to combination therapy with bevacizumab, there is no common link with which to compare this study to the RCT evidence available for lenalidomide.

Details of excluded RCTs can be found in appendix B.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

As discussed earlier, 40 non-RCTs (41 publications) were identified; of these, 9 were published in abstract format, see Table 8. The key data relevant to the decision problem are contained within the phase III studies MM-009 and MM-010. The Taverna et al and Damaj et al papers were assessed as the most relevant information for comparator treatments (see section 6.8).[45, 46] For completeness the remaining non-RCT studies are presented in appendix C.

Table 8: List of relevant non-RCTs

Author, year (reference)	Intervention	Population	Objectives	Justification for inclusion
MM-021[47] (13)	Len/Dex	rrMM patients with ≥1 prior anti-myeloma therapy	To assess the efficacy, safety & pharmacokinetics of lenalidomide plus low-dose dexamethasone in Chinese patients with rrMM.	Met all of the inclusion criteria
Berenson, 2012[48]	Pom/Dex/PLD	rrMM patients with ≥1 prior anti-myeloma therapy	To investigate the safety & efficacy of Pom in combination with IV Dex & PLD using a modified dose and longer 28-day schedule for patients with rrMM	Met all of the inclusion criteria
Ho, 2011 [49]	Cyclo/Bor/(Dex or Predn)	Patients that had received Cyclo/Bor/(Dex or Predn) at Moffitt centre	To report the safety & efficacy of Cyclo/Bor/(Dex or Predn) combination in patients with rrMM	Met all of the inclusion criteria
Hrusovsky, 2010[50]	Bor ± Dex[a]	Patients previously treated with Bor and achieved at least a PR	To evaluate the efficacy & safety of Bor retreatment in patients with relapsed multiple myeloma who had responded to initial Bor treatment.	Met all of the inclusion criteria
Conner, 2008[51]	Bor	Patients retreated with Bor therapy after initial course of Bor.	To describe patterns of retreatment with Bor in a community-based setting & responses to retreatment.	Met all of the inclusion criteria
Kneppers, 2010[52]	Len/Dex	Patients relapsing after an initial response or no response at all on the former treatment	To determine the response & survival in patients who relapsed or were resistant to Thal.	Met all of the inclusion criteria
RETRIEVE[53]	Bor ± Dex[a]	Patient previously achieving ≥PR to prior bortezomib therapy	To evaluate the efficacy & safety of Bor retreatment in patients with MM, who had relapsed/progressed after achieving at least PR to prior Bor-based therapy.	Met all of the inclusion criteria

Author, year (reference)	Intervention	Population	Objectives	Justification for inclusion
Berenson, 2006[54]	Mel/arsenic trioxide/ ascorbic acid	Relapsed or refractory patient to prior anti-multiple myeloma treatment	To investigate the efficacy & safety of MAC combination therapy in a larger cohort of patients with rrMM and the effects on renal function	Met all of the inclusion criteria
GEM-PETHEMA[55]	Len/Dex	lenalidomide treated patients within a compassionate use program	To evaluate the clinical results of Len as a compassionate salvage therapy in rrMM patients	Met all of the inclusion criteria
MM-018[56]	Len/Dex	Patients with progressive disease after ≥2 cycles of prior anti-MM treatment.	To obtain additional data on the safety and efficacy of Len/Dex treatment and to assess the impact on quality of life.	Met all of the inclusion criteria
Guglielmelli, 2011[57]	Len/Dex	Patients previously treated with Thal-based regimen.	To evaluate the impact of Thal therapy on Len response and outcome in rrMM patients.	Met all of the inclusion criteria
Baz, 2012[58]	Pom/Cyclo/Dex	rrMM patients after ≥2 prior therapies and were lenalidomide refractory	To evaluate the safety of adding oral weekly Cyclo to Pom and a more frequent dose of Dex and plan a phase II randomised trial to assess the efficacy of this strategy in rrMM	Met all of the inclusion criteria
Berenson, 2006b[59]	Bor/Mel	Patients with active progression after two prior treatment regimens	To assess the safety, tolerability & response rate in a dose-escalation study of Bor/Mel combination for rrMM	Met all of the inclusion criteria
Damaj, 2012[46]	Ben/Predn	rrMM disease after prior therapies that had to include alkylators, steroids, IMiDs (either Len or thalidomide) and bortezomib.	To evaluate the response rate to bendamustine, the duration of response, PFS & OS.	Met all of the inclusion criteria
Delforge, 2011[60]	Len/Dex	Patients with progressive disease according to EBMT or IMWG criteria.	To report the results of the Revlimid Medical Need Programme, with emphasis on the activity of Len/Dex in Thal & Bor refractory patients.	Met all of the inclusion criteria

Author, year (reference)	Intervention	Population	Objectives	Justification for inclusion
Sood, 2009[61]	Bor ± Dex or Thal or Dox[a]	Relapsed patients following prior bortezomib treatment	To determine the safety & efficacy of Bor retreatment in patients with MM who had previously responded to Bor and to determine the TTP & incidence of SAEs with bortezomib retreatment.	Met all of the inclusion criteria
Klein, 2011[62]	Len/Dex	Patients with rrMM complicated by renal failure	To evaluate the influence of renal impairment & previous therapies in patients with relapsed MM who have been treated with Len	Met all of the inclusion criteria
Dimopoulos, 2012[63]	Len/Dex	rrMM patients	To analyse data on different doses of Dex with Len in rrMM patients	Met all of the inclusion criteria
Falcone, 2012[64]	Bor/Dor/Dex	rrMM patients	To verify the synergistic interaction of Bor/PLD/Dex towards myeloma cells	Met all of the inclusion criteria
Moscetti, 2012[65]	Len/Dex	Overtreated MM patients	NR	Met all of the inclusion criteria
Oehrlein, 2012[66]	Len/Dex	rrMM patients treated with Len/Dex	To analyse the long-term outcome in rrMM patients treated with Len/Dex	Met all of the inclusion criteria
Palumbo, 2012[67]	Pom/Cyclo/Predn	Patients relapsed/refractory to Len	To assess dosing, efficacy and safety of Pom/cyclo/predn in MM patients relapsed/refractory to Len	Met all of the inclusion criteria
Voorhees, 2011[68]	PLD/Bor/ vorinostat	rrMM patients	To evaluate the safety and preliminary efficacy of vorinostat when combined with the PLD and Bor backbone.	Met all of the inclusion criteria
Touzeau, 2012[69]	Len/Dex	Patients older than 74 years treated with Len/Dex for rrMM	To assess the outcome of patients over the age of 75 with rrMM treated with Len/Dex combination therapy	Met all of the inclusion criteria

Author, year (reference)	Intervention	Population	Objectives	Justification for inclusion
Offidani, 2011[70]	Induction therapy Thal/Dex/PLD/ Bor Consolidation Bor/(Dex/Thal) /Dex Maintenance Thal	rrMM patients	To explore the efficacy of Thal, Dex, PLD and Bor combination in rrMM patients	Met all of the inclusion criteria
Schey 2010[71]	Cyclo/Dex/Len	rrMM patients	To determine the MTD of cyclophosphamide when combined with lenalidomide and dexamethasone in rrMM	Met all of the inclusion criteria
Popat 2009[72]	Bor/Mel/Dex MTD: Mel/Bor	Patients with relapsed MM	To determine the efficacy and safety of Bor/Mel combination when Mel is given as a single intravenous dose every 28 days with bortezomib.	Met all of the inclusion criteria
Petrucci 2013[73]	Mel/Bor/Predn	Elderly patients with rrMM	To assess the dosing, efficacy and safety of a lower dose-intensity Mel and Predn schedule plus weekly Bor as salvage treatment for elderly patients with MM and to determine the durations of PFS & OS	Met all of the inclusion criteria
Palumbo 2010[74]	Len/Mel/Predn Thal	rrMM patients	To evaluate the safety and efficacy of salvage therapy with Len, Mel, Predn and Thal in patients with rrMM	Met all of the inclusion criteria

Author, year (reference)	Intervention	Population	Objectives	Justification for inclusion
GIMEMA[75] (Palumbo et al, 2010)	Mel/Predn/ Thal/Def	rrMM patients	To identify the most appropriate dose of defibrotide in combination with Mel Predn and Thal in rrMM patients and to determine its safety and tolerability	Met all of the inclusion criteria
Ciolli 2008[76]	Bor/Dex/Thal Bor/Dex/Thal/ PLD	Advanced MM	To compare the results achieved in two groups of advanced MM patients receiving the same Bor, Thal and Dex regimen with or without PLD	Met all of the inclusion criteria
Chanan-Khan 2009[77]	Bor/PLD/Thal	rrMM patients	To investigate the efficacy of a steroid-free combination including Bor, PLD and Thal among patients with advance stage rrMM	Met all of the inclusion criteria
Palumbo 2008[78]	Bor/Dex/Dox/PLD	Advanced MM	To evaluate the safety and efficacy of the combination of Bor with Dox or PLD and low-dose Dex repeated every 28 days, in patients with rrMM.	Met all of the inclusion criteria
Iida 2010[79]	Len/Dex	Japanese patient with rrMM	To investigate the safety, efficacy and pharmacokinetics of Len in Japanese patients with rrMM	Met all of the inclusion criteria
ECOG E2A02[80]	Bor	High-risk MM	To prospectively evaluate the effect upfront Bor has upon response rate, 1- and 2-year PFS and OS among patients with high-risk MM	Met all of the inclusion criteria
Dimopoulos 2010b[81]	Len/Dex Len/Dex/Bor	Patients with rrMM with impaired renal function	To evaluate the impact of several cytogenetic abnormalities in patients with rrMM who received Len and Dex with or without the addition of Bor	Met all of the inclusion criteria

Author, year (reference)	Intervention	Population	Objectives	Justification for inclusion
Waterman 2011[82]	Dex/Bor/PLD	rrMM patients	To evaluate the efficacy and safety of a more frequent low-dose schedule of PLD, Bor and intravenous Dex for patients with rrMM, many of whom were previously treated with Bor	Met all of the inclusion criteria
Terpos 2008[83]	Bor/Mel/Dex/Thal	rrMM patients	To determine the efficacy and safety of the combination of Bor, Mel, Dex and intermittent Thal and its effect on bone remodelling and angiogenesis in rrMM	Met all of the inclusion criteria
Schwamborn 2011[84]	Len/Dex	rrMM patients	To evaluate the efficacy of treatment of patients with rrMM who could not be treated with the usual dose of Len (25mg per day, for 21 days in a 28-day cycle)	Met all of the inclusion criteria
Taverna 2012[45]	Bor ± Dex or other therapies	rrMM patients	NR	Met all of the inclusion criteria
Berenson, 2008[85]	Bor/Mel	Patients with active progression after two prior treatment regimens	Update result of Berenson 2006b	

Bor, bortezomib; Cyclo, cyclophosphamide; Dex, dexamethasone; Dox, doxorubicin; EBMT, European Society for Blood and Marrow Transplantation ; IMiDs, Immunomodulatory drugs; IMWG, International Myeloma Working Group; Len, lenalidomide; MAC, melphalan/arsenic trioxide/ascorbic acid; Mel, melphalan; MM, multiple myeloma; MTD; maximum tolerated dose; OS, overall survival; PFS, progression-free survival; Pom, pomalidomide, PLD, pegylated liposomal doxorubicin; PR, partial response; Predn, prednisone; RCT, randomised controlled trial; rrMM, relapsed or refractory multiple myeloma; SAEs, serious adverse events; TTP, time to progression; VGPR, very good partial response.

6.3 Summary of methodology of relevant RCTs

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (*www.consort-statement.org*). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, **the information should be tabulated**.

Methods

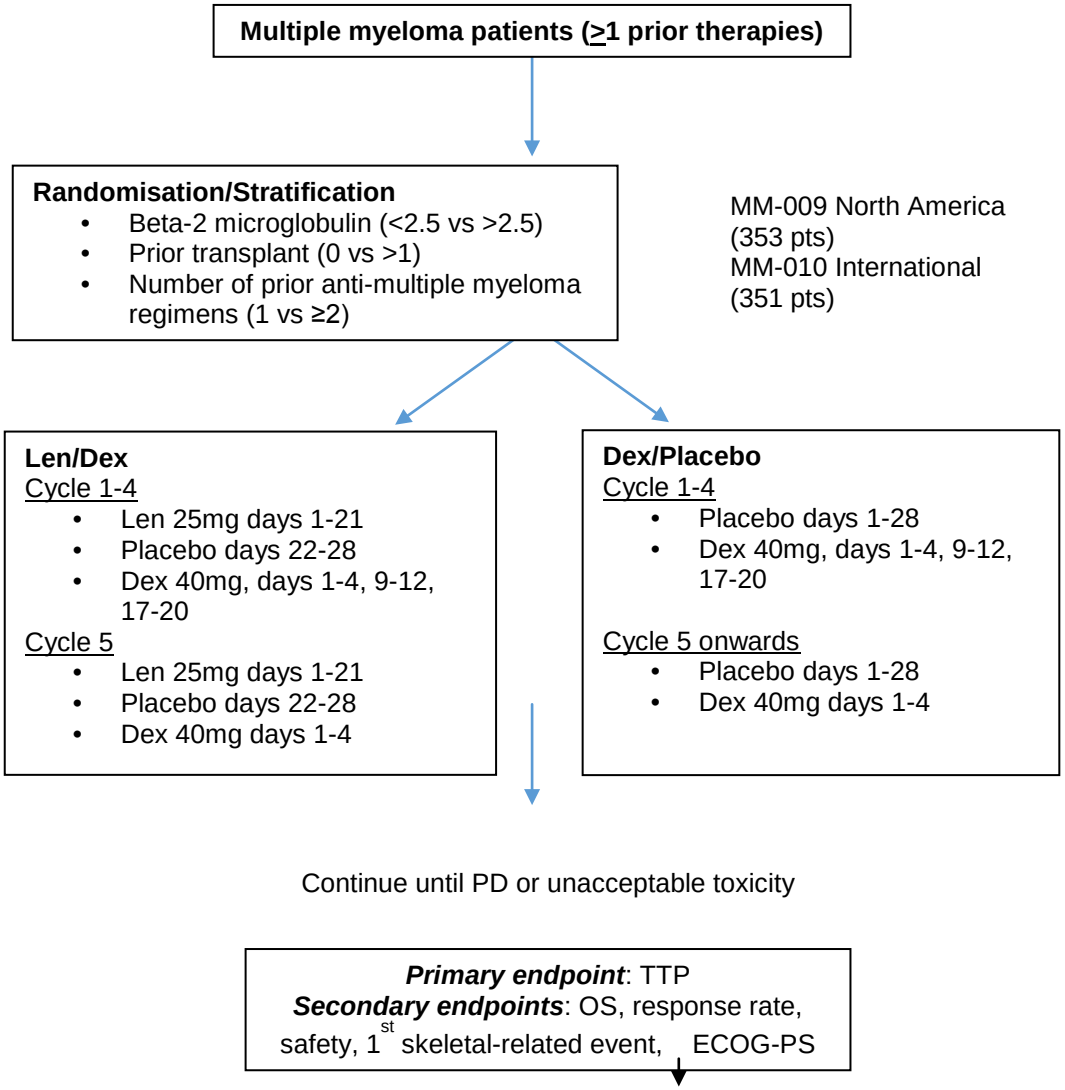
6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

Lenalidomide – MM-009/MM-010

Study design

The MM-009 and MM-010 studies were identically designed multicentre phase III, double-blind, randomised, placebo-controlled clinical trials designed to evaluate the efficacy and safety of Len/Dex compared with Dex in patients with relapsed multiple myeloma (Figure 3). Study MM-009 was conducted in the United States and Canada and enrolled 353 patients. Study MM-010 was conducted in Europe, Israel and Australia and enrolled 351 patients.[86, 87]

Figure 3: Design summary for studies MM-009 and MM-010



EOCG-PS, Eastern Cooperative Oncology Group performance status, OS, overall survival; PD, progressive disease; TTP, time to progression.

Central randomisation was performed with a block size of four and the use of an integrated voice-response system (IVRS). The IVRS ensures that registration and randomisation were performed quickly and conveniently. In order to reduce selection bias, the random assignment of patients to treatment groups was stratified according to the level of serum beta-2 microglobulin (<2.5mg/L versus ≥2.5mg/L), previous stem cell transplantation (none versus ≥1), and the number of previous anti-myeloma therapies (1 versus ≥2). Patients were assigned to receive either Len/Dex or placebo/Dex by randomisation at a 1:1 ratio.

These were double-blind studies. The lenalidomide and placebo capsules were identical in appearance, and the subjects, investigators, other study site

personnel and Celgene personnel who were responsible for the study were blinded to each subject's treatment until the study was unblinded.

Outcomes

The primary outcome for MM-009 and MM-010 was TTP, with a protocol-specified interim analysis planned for when 50% of the subjects had reached the primary endpoint, to determine if the study should be stopped for superiority, futility or unfavourable toxicity. Prospectively-defined secondary analyses of TTP were conducted, according to: the number of lines of prior therapy; whether patients had previously received stem-cell transplantation and chemotherapy; and category of baseline serum beta-2 microglobulin. Post-hoc analyses of outcome according to the type of prior therapy were also undertaken. A number of other sub-group and pooled analyses have been conducted and presented at conferences. These are discussed further in the following sections (sections 6.3.7 and 6.5.1).

Measurable disease was defined as a serum monoclonal protein (M-protein) level of at least 0.5g/dL or a urinary Bence–Jones protein level of at least 0.2g per day. A complete list of patient inclusion/exclusion criteria are described in detail in sections 6.3.3 below.

Power calculation

The number of patients was calculated so that a one-sided log-rank test at the 0.025 level, allowing for one interim analysis, would have a statistical power of 85% to detect a difference between the TTP for each group with a constant hazard ratio of 1.5, reflecting an increase of 50% in the median TTP. The number of events required was 222.

On the basis of the planned accrual rate, a log-rank test of OS that was performed 18 months after the last patient had been enrolled, when 194 deaths were expected, would have a power of 80% to detect a hazard ratio for death of 0.67.

Interim analysis

An interim analysis of safety and efficacy was planned when disease had progressed in 111 patients in both studies MM-009 and study MM-010 (half of the 222 events required for 85% power). The safety and efficacy data were reviewed by an Independent Data Monitoring Committee (IDMC). If the predetermined O'Brien–Fleming boundary for the superiority of Len/Dex over placebo/Dex was crossed, the study would be unblinded at the discretion of the IDMC and patients would be allowed to receive lenalidomide at the time of disease progression or at the investigator's judgment.

Interventions

The selection of combination therapy with Len/Dex was based on the available data regarding the additive or synergistic effects of immunomodulatory drugs (IMiDs) and dexamethasone in the treatment of multiple myeloma at the time the study was initiated.[88-92]

Dexamethasone was adopted as the control arm because it represented an accepted standard or care at the time and other chemotherapy regimens were not considered superior.[93-95]

The use of high-dose dexamethasone as the control therapy allowed for a direct comparison with Len/Dex experimental treatment, enabling evaluation of the contribution of lenalidomide to the combination.

The dose and schedule of dexamethasone administration used in these studies represent a pulse high-dose regimen that is used to treat subjects with advanced multiple myeloma.[91, 94] The intensity of high-dose dexamethasone therapy was decreased after four cycles of treatment. The dose of dexamethasone chosen was considered ethically acceptable as an active comparator.[94]

Timing

Patients received a starting dose of 25mg daily oral lenalidomide or placebo on days 1–21 of each 28-day cycle. All patients also received 40mg of oral dexamethasone on days 1–4, 9–12 and 17–20. After the fourth cycle, 40mg of

dexamethasone was administered on days 1–4. Treatment was continued until the occurrence of disease progression or unacceptable toxicity.

Blood counts and physical examination were performed on days 1, 8 and 15 during cycle 1, days 1 and 15 during cycles 2 and 3; and on day 1 of each cycle thereafter. Serum and urinary protein electrophoresis studies were performed on day 1 of each cycle and at the end of treatment.

Treatment crossover

Patients in the placebo/Dex arm were able to crossover to receive lenalidomide either at study unblinding or on discontinuation of treatment if they had experienced disease progression prior to this point. Interpretation of OS data for placebo/Dex was therefore complicated by this.

Adverse events

Toxic effects were graded according to the National Cancer Institute's Common Toxicity Criteria, version 2.0.[96] In the case of a grade 3 or 4 adverse event, treatment was withheld and restarted at the next lower daily dose. The dose of lenalidomide was modified as follows:

- 15mg (dose level, –1)
- 10mg (dose level, –2)
- 5mg (dose level, –3)

For grade 3 or 4 neutropenia without other toxic effects, the first dose-modification step was:

- Daily granulocyte colony-stimulating factor (G-CSF) at 5µg per kilogram of body weight and 25mg of lenalidomide (dose level –1)
- G-CSF at 5µg/kg and 15mg (dose level, –2)
- G-CSF at 5µg/kg and 10mg (dose level, –3)
- G-CSF at 5µg/kg and 5mg (dose level, –4)

Dose levels –2 to –4 included daily administration of 5µg per kg of G-CSF at the investigator's discretion. Thromboprophylaxis was not required, although it was used on an individual basis.

Modifications in the dose of dexamethasone because of toxic effects were:

- 40mg daily for 4 days every 2 weeks (dose level, –1)
- 40mg daily for 4 days every 4 weeks (dose level, –2)
- 20mg daily for 4 days every 4 weeks (dose level, –3)

Assessment of response

The response of patients was assessed according to the criteria of the European Society for Blood and Marrow Transplantation (EBMT).[97, 98]

Myeloma paraprotein: serum and urine protein electrophoresis were performed at baseline, on day 1 and 15 during the first three cycles, followed by day 1 of each subsequent cycle and at the end of treatment. Quantitative immunoglobulins were determined and serum and urine fixation studies performed at baseline and day 1 of each cycle beginning with cycle 2.

A partial response (PR) was defined as a reduction of M-protein by at least 50% in serum, 90% in urine, or both, as confirmed by at least two electrophoretic measurements. A complete response (CR) was defined as the complete disappearance of M-protein in serum and urine by immunofixation, as confirmed by two measurements and the presence of less than 5% marrow plasma cells; the criteria for near CR (nCR) were identical to those for CR but without confirmation of marrow plasmacytosis of less than 5% or the disappearance of M-protein. The TTP was measured from randomisation to the date of the first assessment showing disease progression. Progressive disease (PD) was defined as an increase of at least 25% in M-protein from nadir; an absolute increase in serum M-protein of more than 500mg/dL, as compared with the nadir value; an absolute increase in urinary M-protein of more than 200mg per 24-hour period; and either a new bone lesion or plasmacytoma (or an increase in the size of such lesions), or a serum calcium level of more than 11.5mg/dL (2.9mmol/L).

Data for patients who died before there was evidence of disease progression were censored at the time of the last evaluation for assessment of protocol-specified TTP. Survival status was determined every 6 months after the

discontinuation of treatment, and OS was calculated as the time from randomisation until death from any cause or the date of the last visit.

Statistical analyses

All primary analyses were based on the intention-to-treat population (ITT), and subgroup analyses were planned on the basis of stratification variables. An unstratified log-rank test was used to compare the time-to-event variables between the two study groups. Both the TTP and OS were estimated by Kaplan–Meier methods. A Cox proportional-hazard regression model was used to assess the effect of demographic and prognostic variables on differences in treatment responses between the two study groups. Exact tests were used to compare response rates. All reported p-values are two-sided.

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Lenalidomide – MM-009/MM-010

Inclusion criteria

Patients were eligible for the study if they had all of the following characteristics[86, 87]:

- Were at least 18 years of age and able and willing to sign an informed consent form
- Had progressive multiple myeloma after at least 2 cycles of anti-myeloma treatment or to have relapsed with progressive disease after treatment
- Had measurable disease that was not resistant to dexamethasone (in patients who had prior dexamethasone treatment)

Patients were considered to have disease that was resistant to dexamethasone if they had undergone disease progression during previous therapy containing high-dose dexamethasone (total monthly dose, >200mg).

Additional eligibility criteria included:

- An Eastern Cooperative Oncology Group performance status (ECOG-PS) of no more than 2
- A serum aspartate aminotransferase or alanine aminotransferase level that was no more than three-times the upper limit of the normal range
- A serum bilirubin level that was less than two-times the upper limit of the normal range
- A serum creatinine level of less than 2.5mg/dL (221µmol/L)
- An absolute neutrophil count of at least 1.0 x 10^9/L
- A platelet count of more than 75,000/mm^3 for patients with less than 50% bone marrow plasma cells and more than 30,000/mm^3 for patients with 50% or more bone marrow plasma cells

Women of child-bearing potential were eligible if they agreed to use contraception, had a negative pregnancy test before enrolment, and agreed to undergo monthly pregnancy testing until 4 weeks after discontinuation of study drug.

Exclusion criteria

Patients who were previously exposed to lenalidomide or whose disease was refractory to dexamethasone were excluded in both studies (MM-009 and MM-010). This was important to ensure there was no bias in the trial. Additional exclusion criteria included:

- Known hypersensitivity (immunologic reaction) to thalidomide or dexamethasone
- History of uncontrollable side effects to dexamethasone
- Use of any standard/experimental anti-myeloma drug therapy within 28 days of initiation of study drug
- Use of any experimental non-drug therapy within 56 days of initiation of study drug treatment

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups.

Lenalidomide – MM-009/MM-010

In MM-009, patients were enrolled from 27 February 2003 at 48 sites in the United States (44 sites) and Canada (four sites). In MM-010, patients were enrolled from 22 September 2003 at 50 sites in Australia (six sites), Europe (41 sites), and Israel (three sites).

Table 9 and Table 10 (below) show patient characteristics for the study subjects enrolled to Len/Dex and placebo/Dex study groups in MM-009 and MM-010. The two treatment groups were well balanced with respect to baseline characteristics including age, sex, stage, ECOG scores, serum beta-2 microglobulin level, and prior therapy. There were no significant differences ($p>0.05$) between the two groups according to a pooled t-test for continuous variables (age, age from diagnosis) and Fisher's exact test for categorical variables.[86, 87]

The number and types of prior anti-myeloma therapies (Table 10) were consistent between MM-009 and MM-010. In MM-009, significantly more of the subjects in the Len/Dex group (80.0%; 136/170) than in the placebo/Dex group (70.2%; 120/171) had received prior therapy with Dex ($p=0.045$; Fisher’s exact test); other than this, no significant differences were observed between the treatment groups in prior anti-myeloma therapies. In MM-010, no significant differences were observed between the Len/Dex and placebo/Dex groups in the number or type of prior anti-myeloma therapies. [86, 87]

Of note are the figures for the number of prior therapies that patients had received on entry into the study. Although there was an inclusion criterion for patients to have received at least one prior therapy, approximately 35% of patients had received one prior therapy only (first relapse), while greater than 65% of patients had received at least two prior therapies. [86, 87]

Table 9: Demographic and clinical characteristics of patients enrolled in MM-009 and MM-010[86, 87]

Characteristic	Study MM-009			Study MM-010		
	Len/Dex N=170	Dex N=171	p-Value [a]	Len/Dex N=176	Dex N=175	p-Value [a]
Age (years)			0.505			0.453
n	170	171		176	175	
Mean	63.3	62.6		62.2	62.9	
SD	9.86	9.61		10.12	8.80	
Median	64.0	62.0		63.0	64.0	
Min, Max	36.0, 86.0	37.0, 85.0		33.0, 84.0	40.0, 82.0	
Sex			0.912			1.000
Male	102 (60.0%)	101 (59.1%)		104 (59.1%)	103 (58.9%)	
Female	68 (40.0%)	70 (40.9%)		72 (40.9%)	72 (41.1%)	
Race/ethnicity			0.455			0.247
White	134 (78.8%)	143 (83.6%)		172 (97.7%)	175 (100.0%)	
Black	25 (14.7%)	17 (9.9%)		2 (1.1%)	0 (0%)	
Hispanic	3 (1.8%)	5 (2.9%)		0 (0%)	0 (0%)	
Asian/Pacific Islander	5 (2.9%)	2 (1.2%)		1 (0.6%)	0 (0%)	
Other	3 (1.8%)	4 (2.3%)		1 (0.6%)	0 (0%)	
Time from first pathologic diagnosis (years)			0.327			0.079
n	170	171		176	175	
Mean	3.6	3.9		4.2	4.8	
SD	2.47	2.76		2.86	3.55	
Median	2.9	3.1		3.4	4.0	
Min, Max	0.5, 14.7	0.4, 19.7		0.4, 15.7	0.3, 26.6	
Baseline multiple myeloma stage			1.000			0.613
I	3 (1.8%)	4 (2.3%)		11 (6.3%)	8 (4.6%)	
II	53 (31.2%)	53 (31.0%)		50 (28.4%)	57 (32.6%)	
III	113 (66.5%)	114 (66.7%)		115 (65.3%)	110 (62.9%)	
Missing	1 (0.6%)	0 (0%)		0 (0%)	0 (0%)	
Multiple myeloma progression manifested [b]						
Rising M-paraprotein levels	161 (94.7%)	162 (94.7%)	1.000	162 (92.0%)	156 (89.1%)	0.367
Worsening lytic bone disease	30 (17.6%)	38 (22.2%)	0.343	43 (24.4%)	56 (32.0%)	0.124
Worsening extramedullary plasmacytoma disease	7 (4.1%)	7 (4.1%)	1.000	5 (2.8%)	7 (4.0%)	0.574

Characteristic	Study MM-009			Study MM-010		
	Len/Dex N=170	Dex N=171	p-Value [a]	Len/Dex N=176	Dex N=175	p-Value [a]
ECOG-PS			0.131			0.596
0	70 (41.2%)	83 (48.5%)		78 (44.3%)	65 (37.1%)	
1	81 (47.6%)	80 (46.8%)		72 (40.9%)	79 (45.1%)	
2	13 (7.6%)	6 (3.5%)		23 (13.1%)	27 (15.4%)	
3	0 (0%)	0 (0%)		0 (0%)	1 (0.6%)	
Missing	6 (3.5%)	2 (1.2%)		3 (1.7%)	3 (1.7%)	
Lytic bone lesions			0.096			0.603
Present	118 (69.4%)	133 (77.8%)		136 (77.3%)	140 (80.0%)	
Absent	51 (30.0%)	38 (22.2%)		40 (22.7%)	35 (20.0%)	
Missing	1 (0.6%)	0 (0%)		0 (0%)	0 (0%)	
Bone marrow aspirate/biopsy						
Cellularity			0.966			0.945
Normal	71 (41.8%)	72 (42.1%)		107 (60.8%)	102 (58.3%)	
Hyperplasia	65 (38.2%)	64 (37.4%)		41 (23.3%)	41 (23.4%)	
Hypoplasia	26 (15.3%)	27 (15.8%)		26 (14.8%)	28 (16.0%)	
Missing	4 (2.4%)	6 (3.5%)		2 (1.1%)	3 (1.7%)	
Percent plasma cells			0.371			0.090
n	165	165		172	169	
Mean	34.5	31.8		36.2	31.1	
SD	28.13	26.79		28.39	26.37	
Median	28.0	25.0		30.0	22.0	
Min, Max	0.0, 95.0	0.0, 100.0		0.0, 100.0	0.0, 100.0	
Baseline beta-2 microglobulin			1.000			0.813
≤2.5mg/L	49 (28.8%)	50 (29.2%)		51 (29.0%)	48 (27.4%)	
>2.5mg/L	121 (71.2%)	121 (70.8%)		125 (71.0%)	127 (72.6%)	

[a] For continuous variables (age, time from first pathologic diagnosis, and percent plasma cells), the p-value is based on a pooled t-test. For the categorical variables, the p-value is based on Fisher's exact test.
[b] More than one category could be selected. Therefore, percentages may total to more than 100%.

Table 10: Prior anti-myeloma therapy – studies MM-009 and MM-010[86, 87]

Type of Therapy	Study MM-009			Study MM-010		
	Len/Dex N=170	Dex N=171	p-Value [a]	Len/Dex N=176	Dex N=175	p-value [a]
No. of prior anti-myeloma therapies			1.000			0.909
1	64 (37.6%)	64 (37.4%)		56 (31.8%)	57 (32.6%)	
2 or 3	106 (62.4%)	107 (62.6%)		120 (68.2%)	118 (67.4%)	
Prior anti-myeloma regimens or SCT			0.491			0.661
1	23 (13.5%)	22 (12.9%)		19 (10.8%)	21 (12.0%)	
2	42 (24.7%)	34 (19.9%)		40 (22.7%)	39 (22.3%)	
3	39 (22.9%)	35 (20.5%)		55 (31.3%)	45 (25.7%)	
>3	66 (38.8%)	80 (46.8%)		62 (35.2%)	70 (40.0%)	
Prior SCT			0.631			0.312
0	68 (40.0%)	69 (40.4%)		77 (43.8%)	81 (46.3%)	
1	28 (16.5%)	18 (10.5%)		31 (17.6%)	21 (12.0%)	
2	25 (14.7%)	28 (16.4%)		30 (17.0%)	23 (13.1%)	
3	15 (8.8%)	17 (9.9%)		4 (2.3%)	4 (4.0%)	
>3	34 (20.0%)	37 (21.6%)		34 (19.3%)	43 (24.6%)	
Prior radiotherapy			0.653			0.305
Yes	60 (35.3%)	65 (38.0%)		62 (35.2%)	52 (29.7%)	
No	110 (64.7%)	106 (62.0%)		114 (64.8%)	123 (70.3%)	
Prior thalidomide therapy			0.586			0.091
Yes	72 (42.4%)	78 (45.6%)		52 (29.5%)	67 (38.3%)	
No	98 (57.6%)	93 (54.4%)		124 (70.5%)	108 (61.7%)	
Prior dexamethasone therapy			0.045			0.650
Yes	136 (80.0%)	120 (70.2%)		116 (65.9%)	120 (68.6%)	
No	34 (20.0%)	51 (29.8%)		60 (34.1%)	55 (31.4%)	
Prior bortezomib (Velcade®) therapy			0.864			1.000
Yes	18 (10.6%)	20 (11.7%)		8 (4.5%)	7 (4.0%)	
No	152 (89.4%)	151 (88.3%)		168 (95.5%)	168 (96.0%)	

SCT, stem cell transplant.
[a] For continuous variables (age, time from first pathologic diagnosis, and percent plasma cells), the p-value is based on a pooled t-test. For the categorical variables, the p-value is based on Fisher's exact test.

Pooled data from studies MM-009 and MM-010

Stadtmauer et al performed a subset analysis of pooled data from MM-009 and MM-010 to evaluate the benefit of using Len/Dex at first relapse.[5] The baseline characteristics and treatment history of these patients are shown in Table 11.

Table 11: Baseline characteristics and treatment history of patients according to number of prior therapies[5]

	Lenalidomide plus dexamethasone		
	1 prior therapy (n=133)	**≥2 prior therapies (n=220)**	**p-value**
Median age, years	62.1	63.1	0.34
Male sex, n (%)	82 (61.7)	128 (58.2)	0.58
Baseline beta-2 microglobulin ≤2.5mg/L, n (%)	47 (35.3)	56 (25.5)	0.054
Baseline beta-2 microglobulin >2.5mg/L, n (%)	86 (64.7)	164 (74.5)	0.054
ECOG score 0–1, n (%)	119 (89.5)	188 (85.5)	0.77
Median time from diagnosis, years (range)	2.2 (0.4–9.7)	4.1 (0.5–15.7)	<0.001
Prior ASCT, n (%)	89 (66.9)	117 (53.2)	0.014
Prior treatment with thalidomide, n (%)	13 (9.8)	114 (51.8)	<0.001
Prior treatment with bortezomib, n (%)	2 (1.5)	25 (11.4)	<0.001

ASCT, autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group.

There were significant differences in the following baseline characteristics between patients who had received one prior therapy compared with those with two or more prior therapies: prior autologous stem cell transplantation (66.9% versus 53.2%; p=0.014); prior treatment with thalidomide (9.8% versus 51.8%; p<0.001); and prior treatment with bortezomib (1.5% versus 11.4%; p<0.001).

The average length of time from diagnosis was also significantly different between patients with one prior therapy (2.2 years) and those who had received two or more prior therapies (4.1 years; p<0.001).

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the

trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice).

Lenalidomide – MM-009/MM-010

The efficacy outcomes used in the phase III studies MM-009 and MM-010 are of an international standard specifically designed for use in multiple myeloma efficacy studies. The design features, endpoints, and plans for interim analysis of these studies and the regulatory strategy for lenalidomide were discussed with the Irish Medicines Board, the Swedish Medicinal Products Agency, the German Federal Institute for Drugs and Medical Devices, and the French Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSAPS).The protocols for MM-009 and MM-010 were subjected to a Special Protocol Assessment review by the US Food and Drug Administration (FDA), Division of Oncology Drug Products. Thus, the planned endpoints, statistical analyses and other methodologies were determined and agreed prior to study initiation with both EU and US regulatory bodies.

A number of post-hoc analyses were undertaken to investigate prognostic variables in multiple myeloma and these are explicitly stated in this submission.

Primary efficacy outcome

The primary efficacy outcome in both MM-009 and MM-010 was time to disease progression (TTP), which was chosen because it is widely accepted as a surrogate endpoint in haematology and oncology studies.

TTP, as specified in the protocol, was calculated as the time from randomisation to the first occurrence of any of the following events:

- Disease progression based on the myeloma response criteria developed by EBMT.[97, 98] The TTP was measured to the date of the first assessment in the series of tests required to determine progression.
- Discontinuation from the treatment phase due to disease progression according to the investigator whether or not confirmed by the EBMT criteria. The TTP was measured to the last date of visit.
- Death due to disease progression during the treatment period. The TTP was measured to the date of death if death occurred on or before treatment discontinuation.

The TTP was censored at the date of last response assessment for subjects who:

- Had not progressed at the time of analysis.
- Withdrew from the treatment phase before documented progression, including those who died of causes not related to multiple myeloma.
- Were given another anti-myeloma therapy without documented progression or intolerable adverse events (for these subjects, the date of their last response assessment prior to taking anti-myeloma therapy was used as the censor date).

For both MM-009 and MM-010, the analysis of TTP was based on the intention-to-treat population. Median follow-up varied depending on the data-cut presented and will be specified in the results tables.

Secondary efficacy outcomes

Progression-free survival

Conducted as part of a supportive analysis for the primary endpoint, progression-free survival (PFS) was calculated as the time from randomisation to documented progression or death due to any cause during the treatment period, whichever occurred first. If withdrawal due to adverse events or change of therapy occurred before documented progression or death, then these observations were censored at the last progression assessment date.

Overall survival

OS is defined as the time from randomisation until death from any cause and was measured in the ITT population. Survival is considered the most clinically meaningful cancer endpoint, and when studies can be conducted to adequately assess OS, it is usually the preferred endpoint. This endpoint is precise and easy to measure, documented by the date of death. OS is generally evaluated in randomised controlled studies. Demonstration of a statistically significant improvement in OS can be considered to be clinically important if the toxicity profile is acceptable, and has often supported new drug approval. Difficulties in performing and analysing survival studies include the requirement for long follow-up periods, large patient numbers and the issue of subsequent cross-over can potentially confounding analyses.

Response rate

Response to therapy was assessed using the myeloma response determination criteria developed by EBMT[97, 98], which are summarised in appendix 10. These criteria provide an international standard for the assessment of treatment response in multiple myeloma, thereby ensuring consistency in the reporting and evaluation of data across study sites. Initially the trial protocols were planning to use the earlier Blade criteria.[97] However, an updated version was released in 2006 and these were used to define the response rate.[98] The response criteria were assessed by collecting blood and urine samples for protein electrophoresis to quantify the proportion of M-protein and immunofixation. New bone lesions and serum calcium levels were also assessed to determine response.

Functioning and quality of life

Other secondary endpoints included the time to first skeletal-related event and time to first decrease in ECOG performance status. These are unpublished data available in the clinical study reports.[86, 87] Both of these are measures of patient quality of life and functioning which may not be captured through response or survival rates.

The time to first worsening of the ECOG performance status was calculated as the time from randomisation to the date of the first worsening compared with the last ECOG evaluation obtained prior to randomisation. Data were censored at the last date that the subject was known to be unchanged or improved from before randomisation. For subjects who had not worsened at the time of the analysis and

for those who were lost to follow-up before worsening the ECOG performance status was documented.

Adverse events

The severity of adverse events and laboratory abnormalities was graded according to National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Version 2.0.[96] The interpretation of these data is not confounded by the conduct of the studies; similar results can realistically be expected to occur on a patient-by-patient basis, with comparable exposure to the study medications in clinical practice.

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken).

Lenalidomide – MM-009/MM-010

The study objectives and sample calculations for both Study MM-009 and Study MM-010 were identical and are presented in Table 12.[86, 87]

Table 12: Summary of statistical analyses in RCTs

Trial no. (reference)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
MM-009 and MM-010 (lenalidomide)	To compare the efficacy of oral lenalidomide in combination with oral pulse high-dose Dex with that of placebo and oral pulse high-dose Dex as treatment for subjects with relapsed or refractory multiple myeloma who have received at least one prior therapy.	All primary analyses and OS were based on the ITT population, and subgroup analyses were pre-planned on the basis of stratification variables (level of beta-2 microglobulin (<2.5mg/L versus ≥2.5mg/L; previous stem-cell transplantation (none versus ≥1); number of previous anti-myeloma therapies (1 versus ≥2)). An unstratified log-rank test was used to compare the time-to-event variables between the two study groups. Both the TTP and OS were estimated by Kaplan–Meier methods. OS was censored at the last date that the patient was known to be alive for patients alive at the time of analysis and for patients who were lost to follow-up before death was documented. Exact tests were used to compare rates of response. Formal statistical hypothesis tests of the superiority of Len/Dex relative to placebo/Dex were conducted at the 2-sided, 0.05 level of significance.	The number of patients was calculated so that a one-sided log-rank test at the 0.025 level, allowing for one interim analysis, would have a statistical power of 85% to detect a difference between the TTP for each group with a constant hazard ratio of 1.5, reflecting an increase of 50% in the median TTP. The number of events required was 222. On the basis of the planned accrual rate, a log-rank test of OS that was performed 18 months after the last patient had been enrolled, when 194 deaths were expected, would have a power of 80% to detect a hazard ratio for death of 0.67. In the case of OS, the studies were unblinded before 194 deaths occurred.	No imputation of values for missing data was performed. Various sensitivity analyses were performed to explore different ways of handling early dropouts. One sensitivity analysis requested by the FDA included counting subjects who withdrew from the study for any reason or who received anti-myeloma therapy during the treatment period as having events on the last assessment day prior to withdrawal from the study or to receiving anti-myeloma medication. All sensitivity analyses confirmed the significant superiority of Len/Dex relative to placebo/Dex. The frequency of missing or out-of window assessments was comparable between the 2 treatment arms, thereby having no effect on the validity of the analysis results.

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Lenalidomide – MM-009/MM-010

Subgroup analyses were conducted for TTP, OS and the rate of response in both the MM-009 and MM-010 studies. Subgroups were analysed on the basis of pre-specified stratification variables including age, gender and the following: the level of beta-2 microglobulin (<2.5mg/L versus ≥2.5mg/L), previous stem-cell transplantation (none versus ≥1), and the number of previous anti-myeloma therapies (1 versus ≥2).

Additional unspecified subgroup analyses were conducted from a pooled analysis of the MM-009 and MM-010 study data. These analyses investigated study outcomes in the following:

- Patients with impaired renal function (as defined by creatinine clearance levels of <30mL/min and <50mL/min)
- Patients with pre-existing peripheral neuropathy (unpublished data provided in confidence by Celgene)
- Eastern Cooperative Oncology Group (ECOG) performance status scores (ECOG= 0 versus ECOG> 0)
- Patients with IgA multiple myeloma
- Patients with a complete or near CR (nCR)
- Patients receiving low-dose dexamethasone in combination with lenalidomide
- Patients receiving prior thalidomide therapy
- Patients receiving prior bortezomib therapy

These subgroups were selected on the basis that they represent important prognostic markers for treatment response in terms of safety and efficacy.

MM-009 and MM-010: Additional post-hoc analyses were conducted using pooled data from both trials. The analyses investigated the following subgroups:

- Elderly patient (<65 years, 65–74 years and aged ≥75 years)
- Patients with impaired renal failure

- Patients who achieved a CR or a very good partial response (VGPR) as best response compared with those who achieved a PR
- Patients continuing treatment after achieving ≥ PR or discontinuing treatment due to adverse events, withdrawal of consent, or for reasons other than disease progression
- First relapse in comparison to later therapy
- Patients previously exposed to thalidomide

Participant flow

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Figure 4: CONSORT flow chart for MM-009[99]

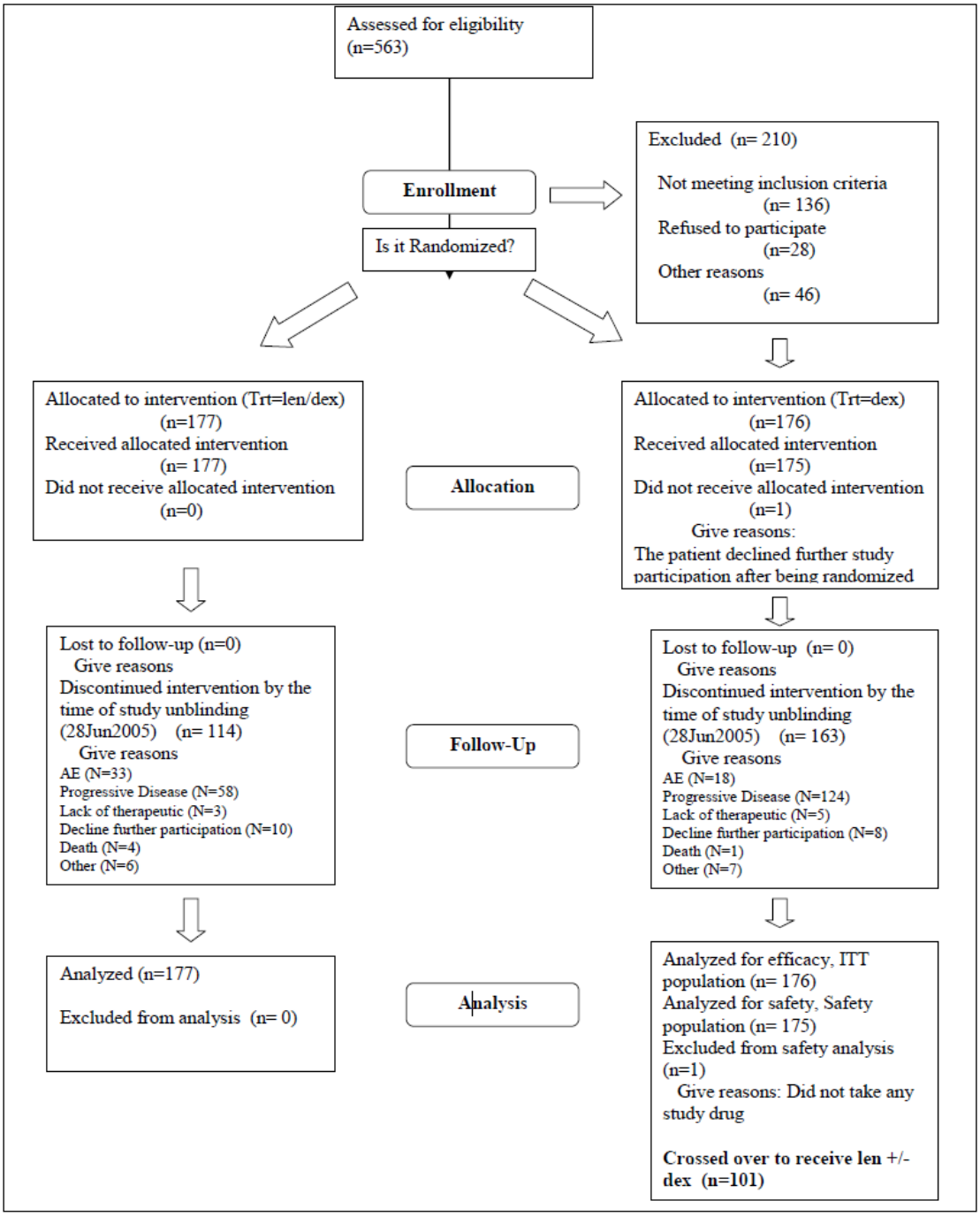
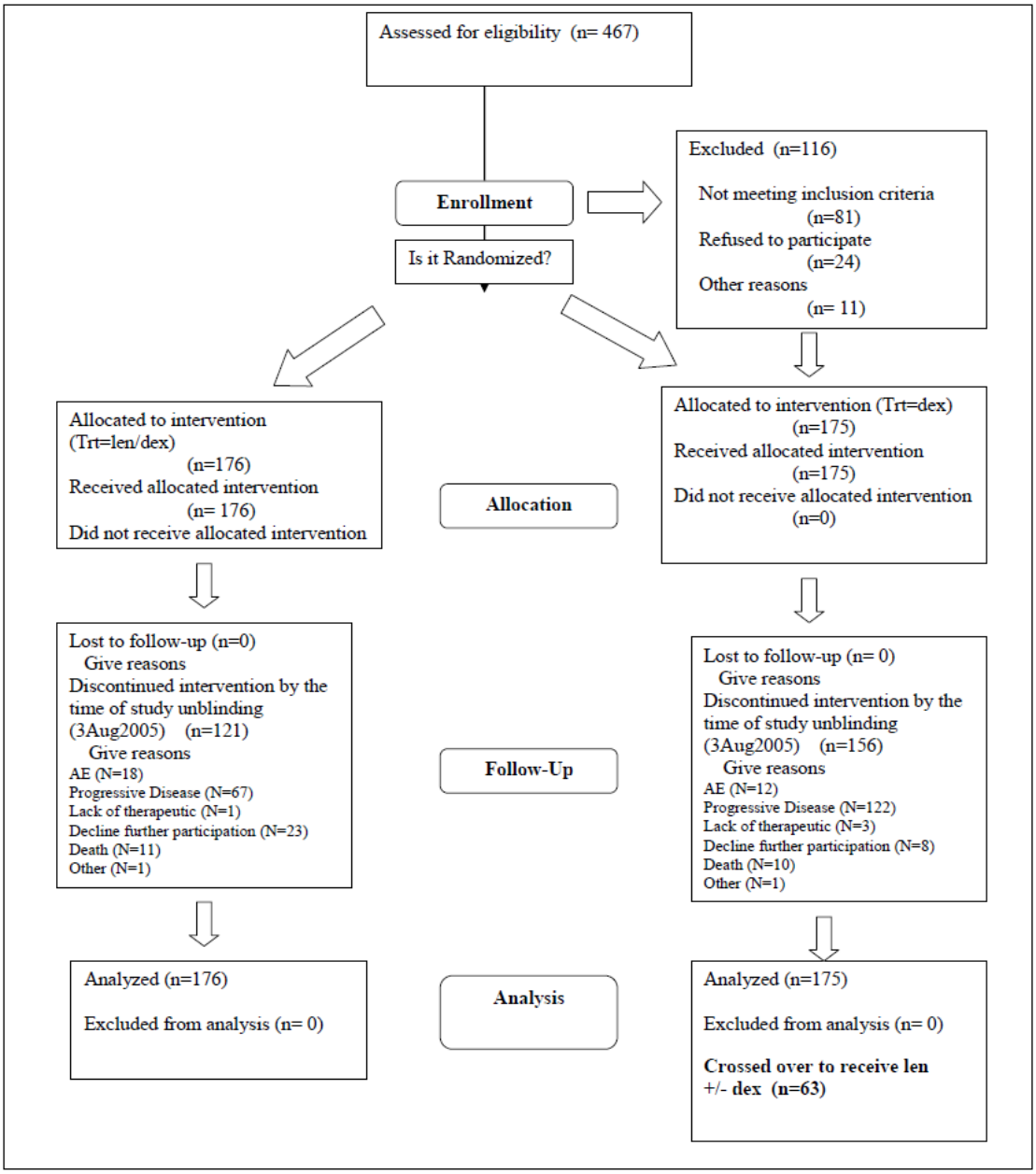


Figure 5: CONSORT flow chart for MM-010[99]



6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG.

Quality assessment results for relevant RCTs are shown in full in section 10.3, appendix 3.

Table 13: Quality assessment results for RCTs

Trial no. (reference)	MM-009 and MM-010
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	Not reported
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
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

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.

Summary of key results of the relevant RCTs

- Studies MM-009 and MM-010, which encompassed a total of 704 patients, demonstrated that Len/Dex significantly increased response rates, TTP and OS in multiple myeloma patients who had ≥1 prior therapy.[40, 41]
- Overall response rate of multiple myeloma patients treated with Len/Dex was approximately three times greater than with placebo/Dex MM-009: 61.0% versus 19.9%, p<0.001) and (MM-010: 60.2% versus 24.0%, p<0.001). [40, 41]
- Median TTP was more than doubled with Len/Dex than placebo/Dex (MM-009: 11.1 versus 4.7 months, p<0.001) and (MM-010: 11.3 versus 4.7 months, p<0.001). [40, 41]
- Pooled analysis of data from studies MM-009 and MM-010 (median follow-up of 48 months) showed that median OS was significantly longer with Len/Dex than placebo/Dex (38.0 versus 31.6 months; p=0.045).[32]
- Subset analysis of pooled data from studies MM-009 and MM-010 comparing patients who received Len/Dex after one prior therapy compared to later in therapy report TTP (17.1 months versus 10.6 months; p=0.026), PFS (median of 14.1 months versus 9.5 months; p=0.047) and OS (median OS of 42.0 versus 35.8 months; p=0.041).[5]
- A patient-level analysis of data from both studies in second-line patients only showed median PFS was longer in the Len/Dex group (16.6 months, 95% CI 11–36.8 months) than in the placebo/Dex group (16.6 versus 4.6 months, p<0.0001) and a numerically higher median OS in the Len/Dex group (50.1 months, 95% CI 8.3–32.5 months) compared to the placebo/Dex group (37.6 months, 95% CI 6.5–21.5 months.[100]

Lenalidomide – MM-009/MM-010

The data from MM-009 and MM-010 presented here were derived from multiple sources. The majority of the analyses are available from the published sources outlined in appendix E. However, to supply the full data requested above it was necessary to use additional sources including the clinical study reports (CSRs) and documents submitted as part of the marketing authorisation application for lenalidomide. In addition for certain outcomes it was necessary to consult the cleaned statistical tables.

Appendix E contains the sources and dates of the various data-cuts.

Interim analysis, study duration and unblinding

Because the O'Brien–Fleming boundary for the superiority of Len/Dex over Dex was crossed at the interim analysis, the IDMC recommended that the study be unblinded.

In MM-009, patients were enrolled from 27 February 2003. The study was unblinded on 28 June 2005. In MM-010, patients were enrolled from 22 September 2003. The study was unblinded on 3 August 2005.

Primary and secondary efficacy analyses were conducted on data from all patients (i.e., ITT population) randomised in study MM-009 (N=353) and study MM-010 (N=351). The O'Brien–Fleming boundary for the superiority of lenalidomide over placebo was crossed at the interim analysis in both studies.

TTP results – primary outcome

Interim TTP

The preplanned interim analyses of both MM-009 and MM-010 occurred when half of the specified disease progressions had occurred i.e. studies were to end when 80% of the patients progressed; therefore, the interim analyses occurred when 40% of the total patients had progressed. The results of TTP at the interim phase are presented in Table 14.

Table 14: Protocol-defined interim analysis (ITT population) of the primary outcome (TTP) from MM-009 and MM-010[2]

		Study MM-009		Study MM-010	
		Len/Dex	Dex	Len/Dex	Dex
TTP Progressed Censored	N n (%) n (%)	170 44 (25.9) 126 (74.1)	171 98 (57.3) 73 (42.7)	176 39 (22.2) 137 (77.8)	175 99 (56.6) 76 (43.4)
	Median (weeks) [95% CI]	41.1 [30.3, NE]	20.1 [16.7, 24.1]	NE [36.1, NE]	20.1 [20.0, 22.1]
Hazard ratio [95% CI]		3.073 [2.149, 4.395]		3.246 [2.239, 4.708]	
Log-rank test p value		< 0.001		< 0.001	

ITT, intention to treat; TTP, time to progression; NE, not estimable.
Data from 12 subjects at investigative site #142 were not reviewed or included in the analysis due to sequestering of the case report forms (CRFs) by this institution. The institution decided to temporarily put a halt to all clinical trial activities of one investigator for unspecified reasons. At the time, the original case report forms were therefore unavailable and only uncertified copies were obtained – as validity of these copies was unclear, the CRFs for these 12 patients were excluded from the original analysis. Subsequently, the institution released the CRFs, which were included in later analyses of the trial data.

TTP at unblinding

The TTP outcomes of MM-009 and MM-010 at study unblinding are presented in Table 15.

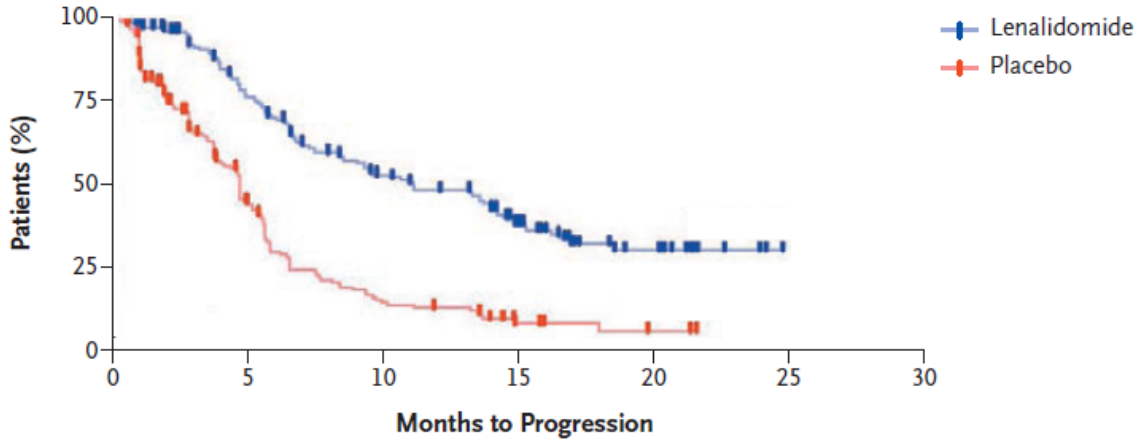
Table 15: Study unblinding analysis (ITT population) of the primary outcome (TTP) –data cut-off to June (MM-009)/August (MM-010) 2005[2]

	Statistic	Study MM-009		Study MM-010	
		Len/Dex	Dex	Len/Dex	Dex
TTP Progressed Censored	N n (%) n (%)	177 92 (52.0) 85 (48.0)	176 132 (75.0) 44 (25.0)	176 82 (46.6) 94 (53.4)	175 142 (81.1) 33 (18.9)
Overall TTP (weeks)	Median [95% CI] [a]	48.1 [36.9, 1.4]	20.1 [16.7, 23.1]	48.7 [40.9, 72.1]	20.1 [18.1, 20.7]
Hazard Ratio [95% CI] [b]		2.822 [2.146, 3.701]		2.850 [2.159, 3.762]	
Log-rank Test p-Value [c]		< 0.001		< 0.001	

CI, confidence interval.
Percentages are based on the number of treated subjects. The median in this table is based on Kaplan–Meier estimate, and the mean is the univariate mean without adjusting for censoring.
[a] 95% confidence intervals about the median overall time to progression.
[b] Based on a proportional hazards model comparing the hazard functions associated with the treatment groups (Len/Dex:/Dex)
[c] The p value is based on the a one-tailed unstratified log rank test of survival curve differences between the treatment groups.
Median follow up: 17.1 months for MM-009 (n=76), 16.7 months for MM-010 (n=74), 16.9 months for combined (n=150).

In MM-009, Len/Dex was associated with a significantly longer median TTP (11.1 months) compared to placebo/Dex (4.7 months) (hazard ratio= 2.82; 95% CI: 2.146, 3.701; P<0.001) (Figure 6). Results for TTP are based on data obtained prior to unblinding upon reaching the O'Brien–Fleming boundary.

Figure 6: MM-009 Kaplan–Meier curves of TTP at study unblinding[41]

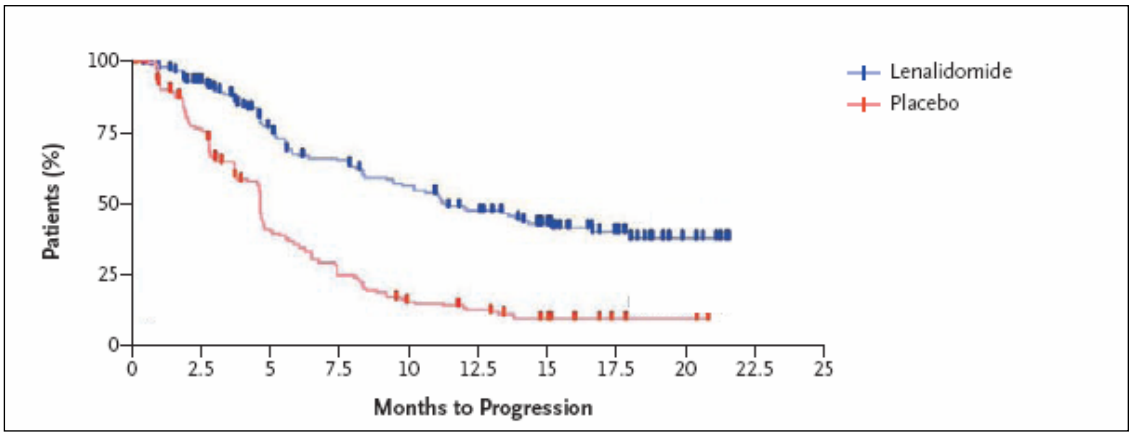


ITT, intention to treat; TTP, time to progression.

Curves show TTP for the ITT population (a median of 11.1 months in the lenalidomide (Len/Dex) group and 4.7 months in the placebo (Dex) group, p<0.001 by the log-rank test).

In MM-010, Len/Dex was associated with a significantly longer median TTP (11.3 months) compared to placebo/Dex (4.7 months) (hazard ratio = 2.85; 95% CI: 2.16-3.76; P<0.001) (Figure 7).

Figure 7: MM-010 Kaplan–Meier curves of TTP at study unblinding[40]



ITT, intention to treat; TTP, time to progression.

Estimates of the median TTP for the ITT population: 11.3 months in the lenalidomide (Len/Dex) group and 4.7 months in the placebo (Dex) group (p<0.001 by the log-rank test).

Pooled analysis studies MM-009 and MM-010

Dimopoulos et al conducted a pooled analysis of efficacy data from Studies MM-009 and MM-010, which also includes long-term findings.[32] This analysis encompassed 353 Len/Dex patients and 351 placebo/Dex patients. The pooled efficacy results of this analysis are summarised in Table 16.

Table 16: Response rates, TTP, PFS and OS[32]

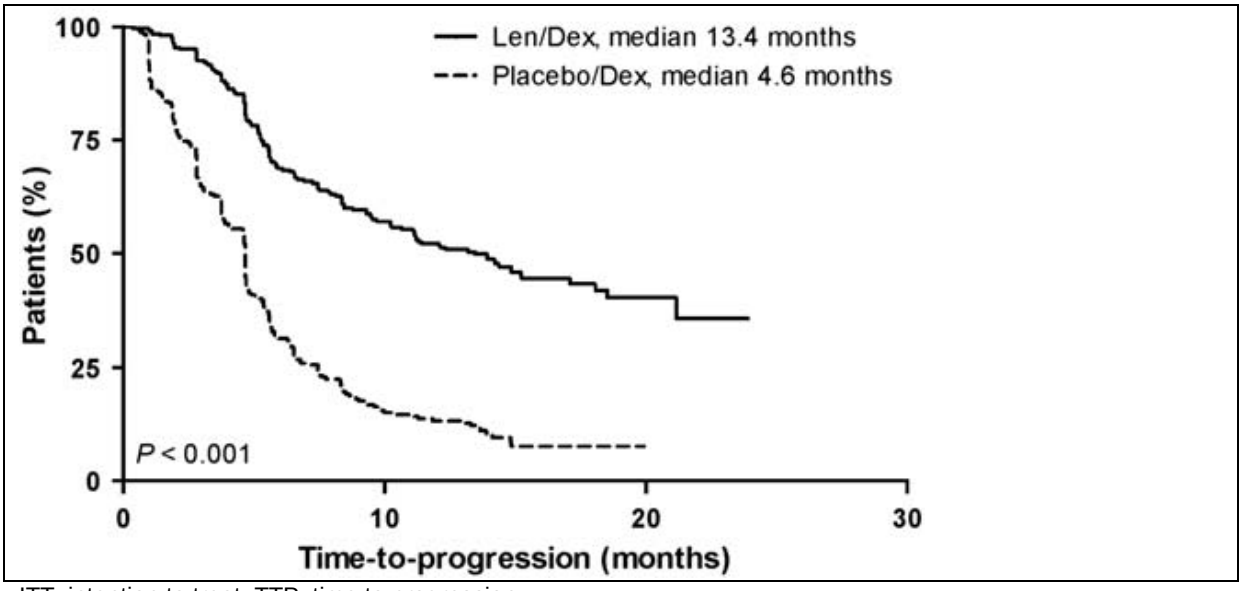
	Len/Dex (n=353)	Dex (n=351)	p value
Up to unblinding (median 17.5 months) Response rate, %			
ORR	60.6	21.9	<0.001
CR	15.0	2.0	<0.001
VGPR	17.3	2.8	
PR	28.3	17.1	
Median TTP, months	13.4	4.6	<0.001
Median DoR, months	15.8	7.0	<0.001
Median PFS, months	11.1	4.6	<0.001
Extended FU (median 48 months) Median OS, months	38.0	31.6	0.045

CR, complete response; DoR, duration of response; FU, follow-up; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TTP, time-to-progression; VGPR, very good partial response.

Pooled analysis: TTP at study unblinding

Up to study unblinding (median follow-up of 17.5 months), pooled analysis of the two studies demonstrated that TTP was significantly longer in patients treated with Len/Dex than in those treated with placebo/Dex (median of 13.4 versus 4.6 months, respectively; p<0.001; Figure 8, Table 16).[32]

Figure 8: Kaplan–Meier estimate of TTP in the ITT population[32]



ITT, intention to treat; TTP, time to progression.
The estimate of TTP for the ITT population of the lenalidomide plus dexamethasone and placebo groups.
Len/Dex denotes lenalidomide plus dexamethasone; Placebo/Dex denotes placebo plus dexamethasone.
Survival curves were compared using log-rank test stratified by study (p<0.001).

Progression-free survival results

PFS at study unblinding

PFS was evaluated as part of the supportive analysis for the primary outcome, TTP. The PFS outcomes of MM-009 and MM-010 at study unblinding were very similar and are presented in Table 17:

In MM-009, Len/Dex was associated with a significantly longer median PFS (41.1 weeks) compared to placebo/Dex (20.1 weeks) (hazard ratio= 2.97; 95% CI: 2.089, 4.222; p<0.001).

In MM-010, Len/Dex was associated with a significantly longer median PFS (not yet reached) compared to placebo/Dex (20.1 weeks) (hazard ratio = 2.567; 95% CI: 1.834–3.592; p<0.001).

Table 17: Summary of PFS (ITT population) – MM-009 and MM-010[101]

	Statistic	Study MM-009		Study MM-010	
		Len/Dex	Dex	Len/Dex	Dex
PFS [a]	N	170	171	176	175
Progressed	n (%)	46 (27.1)	99 (57.9)	51 (29.0)	104 (59.4)
Censored	n (%)	124 (72.9)	72 (42.1)	125 (71.0)	71 (40.6)

	Statistic	Study MM-009		Study MM-010	
		Len/Dex	Dex	Len/Dex	Dex
Overall PFS (wk)	Median [b] [95% CI] [c]	41.1 [29.4, NE]	20.1 [16.7, 24.1]	NE [34.1, NE]	20.1 [19.7, 21.7]
	Mean [d] SD Min, Max	21.2 13.39 0.0, 60.1	15.7 11.17 0.0, 57.0	19.8 10.93 0.0, 44.7	16.4 10.03 0.3, 48.1
Hazard ratio [95% CI] [d]		2.970 [2.089, 4.222]		2.567 [1.834, 3.592]	
Log-rank Test p-value [e]		<0.001		<0.001	

PFS, progression-free survival; NE = not estimable.
[a] Calculated as the time from randomisation to documented progression or death due to any cause, whichever occurred first. If withdrawal due to adverse events or change of therapy occurred before documented progression or death, then these observations were censored at the last progression assessment date.
[b] The median is based on the Kaplan–Meier estimate, and the mean is the univariate mean without adjusting for censoring (i.e., the mean values represent mean PFS documented to date as of the data cut-off date, without consideration of the fact that a substantial number of subjects who had not yet progressed were continuing in the study).
[c] Ninety-five percent confidence intervals about the median overall PFS.
[d] Based on a proportional hazards model comparing the hazard functions associated with the treatment groups (Len/Dex: placebo/Dex).
[e] The p-value is based on a one-tailed unstratified log rank test of survival curve differences between the treatment groups.

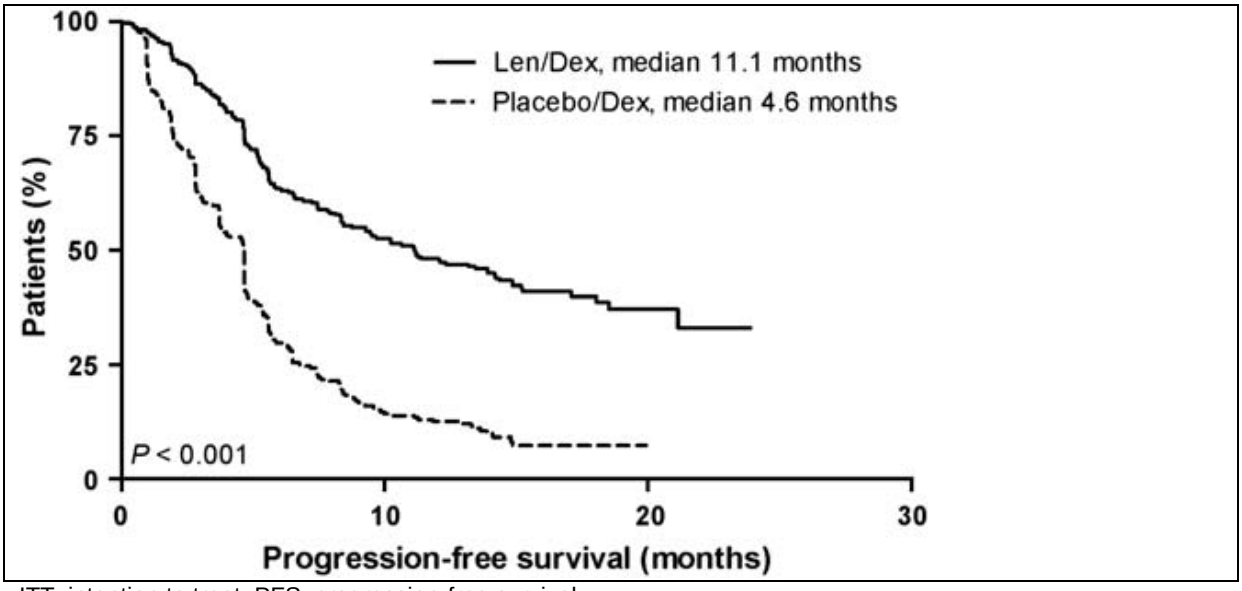
The median PFS in each treatment group in each study was comparable to the median TTP based on the protocol-specified definition of TTP. In both studies, PFS was significantly longer in the Len/Dex group than in the placebo/Dex group ($p<0.001$; one-tailed unstratified log rank test of the survival curve difference between treatment groups); overall, the PFS data from study MM-009 were comparable with those from study MM-010. Based on the hazard ratios, subjects in the placebo/Dex group were 2.6 to 3.0 times more likely than those in the Len/Dex group to experience disease progression or death at any time during the treatment phase.

The analyses confirmed the results that were observed with protocol-specified analysis of TTP. Significant differences between the treatment groups in favour of the Len/Dex combination were observed across both studies and were comparable in magnitude.

Pooled analysis: PFS at study unblinding

The pooled analysis also revealed that up to study unblinding PFS was significantly longer in Len/Dex patients than in Dex patients (median of 11.1 versus 4.6 months, respectively; $p<0.001$; Figure 9, Table 16).[32]

Figure 9: Kaplan–Meier estimate of PFS in the ITT population[32]



ITT, intention to treat; PFS, progression-free survival.
The estimate of progression-free survival for the intent-to-treat population of the lenalidomide plus dexamethasone-placebo groups. Len/Dex denotes lenalidomide plus dexamethasone; Placebo/Dex denotes dexamethasone-placebo. Survival curves were compared using log-rank test stratified by study (p<0.001).

Furthermore, time to first response was similar in patients treated with Len/Dex than in those treated with placebo/Dex (median of 1.9 versus 2.0 months, respectively). However, Len/Dex patients had a substantially longer duration of response than placebo/Dex patients (median of 15.8 versus 7.0 months, p<0.001; Table 16: Response rates, TTP, PFS and OS[32]).

The median duration of treatment was 10.1 months for patients treated with Len/Dex compared with 5.3 months for patients treated with placebo/Dex (p<0.0001). The pooled overall response rate was significantly higher in Len/Dex patients than placebo/Dex patients (60.6% versus 21.9%, respectively; p<0.001; Table 16: Response rates, TTP, PFS and OS[32]). Among Len/Dex patients, CR was observed in 15.0% and VGPR in 17.3%, which was significantly higher compared with placebo/Dex patients (2.0 and 2.8%, respectively; p<0.001 for the between-treatment comparison for CR + VGPR).

Overall survival results

Interim OS

Data presented in the clinical overview submitted as part of the marketing authorisation application for lenalidomide show that in MM-009, as of the cut-off date of 15 July 2004[101]:

- 9.4% (16/170) of the Len/Dex-treated subjects had died
- 8.8% (15/171) of the placebo/Dex-treated subjects had died

In MM-010, data presented up to the cut-off date of 15 September 2004 show that:

- 15.9% (28/176) of the Len/Dex-treated subjects had died
- 16.0% (28/175) of the placebo/treated subjects had died

Therefore, at this stage of follow-up, relatively few deaths occurred in either treatment group in MM-009 or MM-010 and consequently, no significant differences were observed between the Len/Dex and placebo/Dex groups with respect to OS.

OS at unblinding

With a greater duration of follow-up, data presented as part of the scientific discussion in the EPAR demonstrated a significant survival advantage for Len/Dex relative to placebo/Dex in MM-009.[2] At this time, 37 (20.9%) of the 177 Len/Dex-treated patients, compared with 62 (35.2%) of the 176 placebo/Dex-treated patients, had died. At this time, no significant difference in OS had been observed between the Len/Dex and the placebo/Dex-treated patients in MM-010 (47 and 59 deaths, respectively), due to the shorter study duration of follow-up.

Updated OS after study unblinding as of May 2006

The median OS is shown in Table 18 and represents data analysed as of May 2006 for both studies – a time from study initiation of 3 years and 3 months for MM-009 and 2 years and 8 months for MM-010.[102] Kaplan–Meier curves for OS are shown for MM-009 and MM-010 in Figure 10 and Figure 11 below, respectively.

Both studies continued to show significant improvement with Len/Dex compared with Dex with respect to median OS. In MM-009, the estimated median OS in the Len/Dex arm was 29.6 months, versus 20.5 months for placebo/Dex (hazard ratio = 0.44; 95% CI: 0.30- 0.65; $p<0.001$). These data represent a 9-month increment in median OS for patients in the Len/Dex versus the placebo/Dex arm.

Median OS for MM-010 was not estimable at this time in the Len/Dex arm and was 20.6 months among those who received placebo/Dex. Although median OS was not

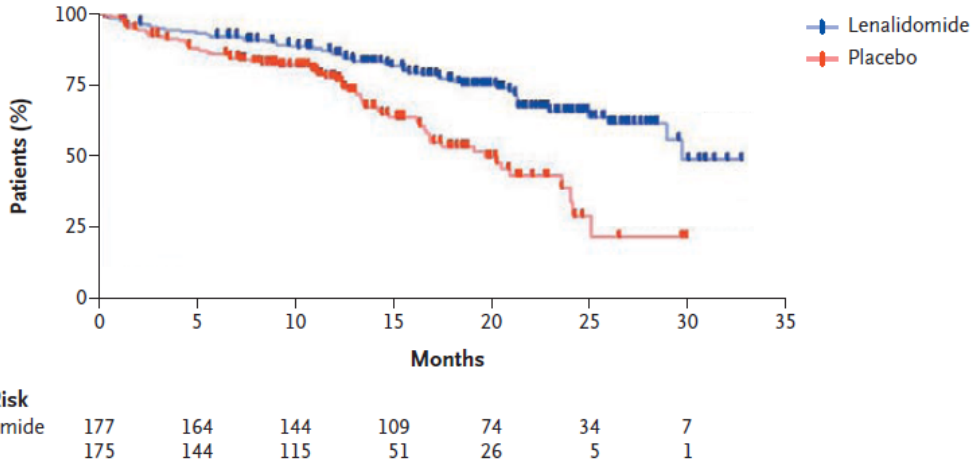
estimable for Len/Dex, it was still significantly higher than for placebo/Dex (hazard ratio = 0.66; 95% CI: 0.45-0.96; p=0.03).

Table 18: Median OS following treatment with Len/Dex or placebo/Dex in the MM-009 and MM-010 trials among patients treated with one prior therapy – ITT population[40, 41]

Characteristic	MM-009		MM-010	
	Len/Dex	Dex	Len/Dex	Dex
Died, n (%)	49 (27.7)	63 (35.8)	47 (26.7)	60 (34.3)
Median OS (months)	29.6	20.2	NE	20.6
Hazard ratio	0.44		0.66	
95% CI	0.30–0.65		0.45–0.96	
P	<0.001		0.03	

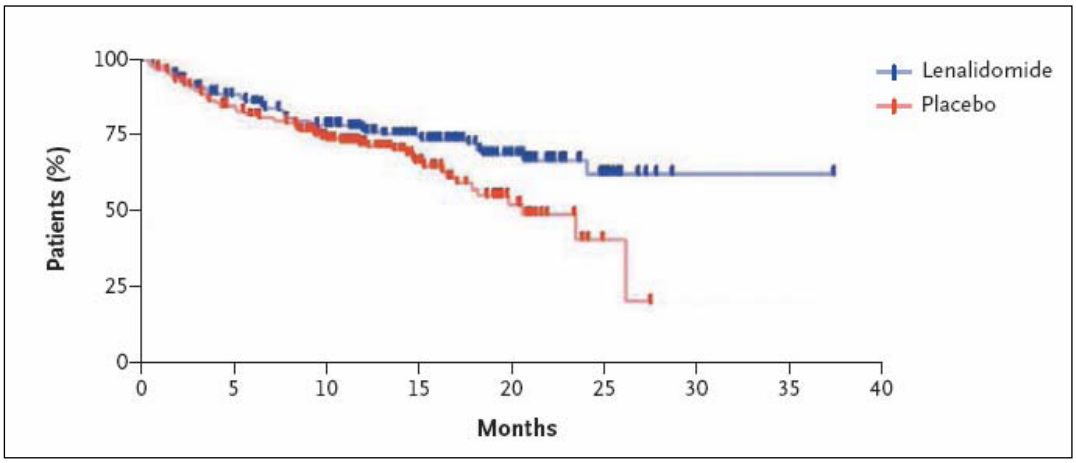
CI, confidence interval: NE, not estimable; ITT. Intention to treat; OS, overall survival. Data analysed as of May 2006 for both studies – a time from study initiation of 3 years and 3 months for MM-009 and 2 years and 8 months for MM-010. Median follow-up at this time-point is 17.1 months for MM-009 and 16.5 months for MM-010.

Figure 10: Kaplan–Meier curves for OS for all patients in MM-009 as of May 2006 for the ITT population[41]



ITT, intention to treat, OS, overall survival.
Estimates of the median OS for the ITT population: 29.6 months in the lenalidomide (Len/Dex) group and 20.2 months in the placebo/Dex group (p<0.001 by the log-rank test).

Figure 11: Kaplan–Meier curves for OS for all patients in MM-010 as of May 2006 for the ITT population



ITT, intention to treat, OS, overall survival.
Estimates of the median OS for the ITT population: not yet reached in the lenalidomide (Len/Dex) group and 20.6 months in the placebo/Dex group (p<0.001 by the log-rank test).

Update on OS: International Myeloma Workshop 2007

In June 2007, an updated median OS was presented at the International Myeloma Workshop.[103] This combined analysis, with follow-up to January 2007, showed that the OS had extended to 35 months in the Len/Dex arm versus 31 months in the placebo/Dex arm (p=0.021).

Perspectives on treatment crossover and OS in MM-009 and MM-010

The estimated median OS of patients in the placebo/Dex arms increased with extended follow-up of the two trials. This phenomenon could be attributed to the small number of deaths among these patients at the point the studies were unblinded and the fact that 170 out of 351 patients in the placebo/Dex arms subsequently went on to receive additional lenalidomide (as per the regimen given to patients in the Len/Dex arms). Both of these factors would allow the estimated median to change over time.

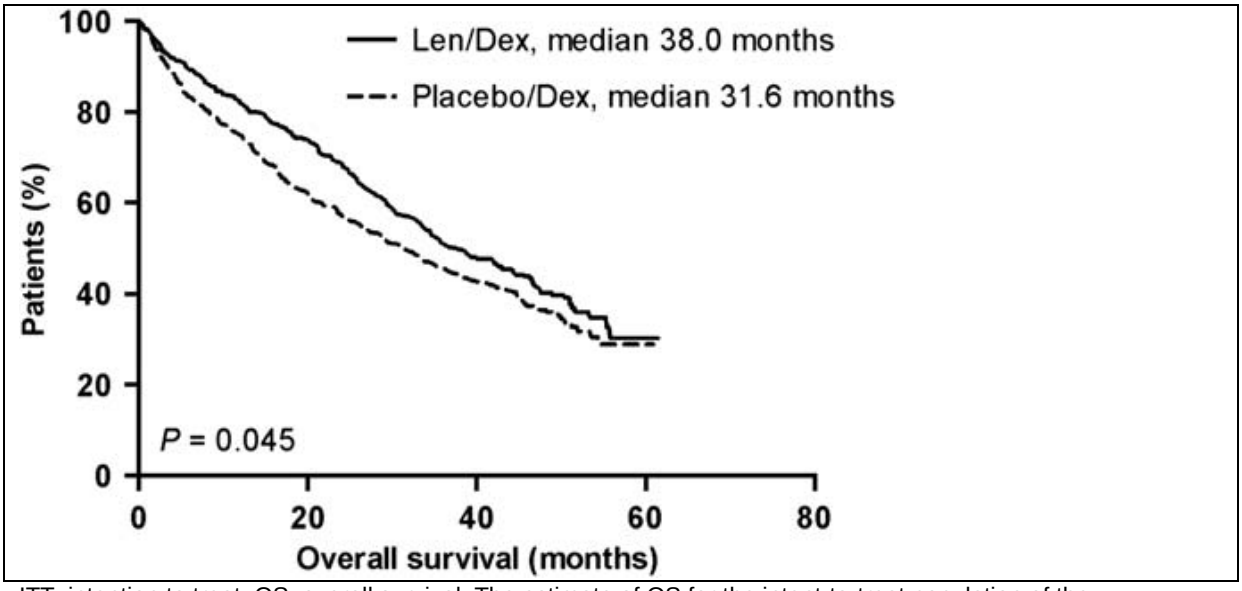
The median OS of patients in the placebo/Dex arms is higher than would be expected. Historical retrospective analyses indicate that the median OS from first relapse is in the region of 14–17 months in patients with multiple myeloma.[104, 105]

Further updated OS analysis is available as a pooled analysis later in this section.

Pooled analysis: Long-term efficacy – OS

After a median follow-up of 48 months, 199 (56.4%) Len/Dex patients had died, compared with 219 (62.4%) placebo/Dex patients. OS was significantly longer in patients treated with Len/Dex than in those treated with placebo/Dex (median of 38.0 versus 31.6 months, respectively; p=0.045; Figure 12, Table 16).[32]

Figure 12: Kaplan–Meier estimate of OS in the ITT population[32]



ITT, intention to treat; OS, overall survival. The estimate of OS for the intent-to-treat population of the lenalidomide plus dexamethasone and dexamethasone-placebo groups. Len/Dex denotes lenalidomide plus dexamethasone; Placebo/Dex denotes dexamethasone-placebo. Survival curves were compared using log-rank test stratified by study (p=0.045).

The Cox proportional hazards regression model for multivariate analysis showed that treatment remained a highly significant predictor of OS (p=0.0008, in favour of Len/Dex). In addition, baseline beta-2 microglobulin levels higher than 2.5mg/L, a baseline ISS (International Staging System) score >1, a high baseline percentage of plasma cells and more than one earlier anti-myeloma treatment were among significant predictors of short OS after controlling for treatment factor (Table 19).

Table 19: Predictors of OS in all patients (Cox regression model)[32]

	Hazard ratio (95% CI)	p-value
Treatment (Placebo/Dex versus Len/Dex)	1.4 (1.2–1.7)	0.0008
Baseline plasma cells percentage (high versus low)	1.0 (1.0–1.0)	<0.0001
High baseline b2-microglobulin (>2.5 versus ≤2.5mg/l)	1.6 (1.2–2.1)	<0.0022
Duration of multiple myeloma	0.9 (0.9–1.0)	0.0008

	Hazard ratio (95% CI)	p-value
Lytic bone lesion at baseline (Yes versus No)	1.3 (1.0–1.6)	0.064
Number of earlier anti-myeloma therapies	1.2 (1.0–1.3)	0.026
Previously treated with HDT/SCT (Yes versus No)	1.2 (1.0–1.5)	0.053
Earlier dexamethasone therapy (Yes versus No)	1.3 (1.1–1.7)	0.017
ISS score at baseline (III versus II versus I)	1.5 (1.3–1.7)	0.0001
CI, confidence interval; HDT, high-dose therapy; ISS, International Staging System; OS, overall survival; SCT, stem cell transplant.		

Of the 351 placebo/Dex patients, 167 (47.6%) received lenalidomide-based therapy after unblinding of the study or following disease progression. Of those, 147 (88%) patients crossed over to lenalidomide alone after disease progression before study unblinding and 20 (12%) crossed over to Len/Dex after the official study unblinding; median time to crossover was 9.6 months. Of the 20 patients who received Len/Dex after study unblinding, 6 (30.0%) did so immediately after study unblinding and 14 (70.0%) crossed over after disease progression. Of the 32 placebo/Dex patients ongoing at study unblinding, 12 did not cross-over to Len/Dex (3 remained on the dexamethasone regimen and subsequently progressed; the remaining 9 patients were either responding or in the plateau phase at the time of data cut-off). After the crossover to a lenalidomide-based therapy, a ≥PR was achieved in 53 (31.7%) patients who were previously randomised to a placebo/Dex regimen. By comparison, in studies MM-009 and MM-010, 61% and 60.2%, respectively, of Len/Dex patients achieved a response of ≥PR.

Response to therapy

Responses at study unblinding

The ITT myeloma response rates of patients treated with Len/Dex versus placebo/Dex during studies MM-009 and MM-010 are presented in Table 20. These data were taken from the scientific discussion in the EPAR and are reproduced in the primary publications.[2, 40, 41] The median follow-up was 17.6 months for MM-009 and 16.4 months for MM-010.

The overall response rate seen in MM-009 (defined as complete, near-complete, or partial response) was significantly higher for Len/Dex- treated patients in comparison to those treated with placebo/Dex (61.0% versus 19.9%, p<0.001). There were also

more patients who had a CR in the Len/Dex arm (14.1%) compared to placebo/Dex (0.6%) (p<0.001).

The overall response rate for study MM-010 was significantly higher for Len/Dex-treated patients in comparison to placebo/Dex-treated patients (60.2% versus 24.0%, p<0.001). There were also more patients who had a CR in the Len/Dex arm (15.9%) compared to the placebo/Dex arm (3.4%) (p<0.001). These findings are very similar to those of study MM-009 outlined in the previous paragraph.

Table 20: Studies MM-009 and MM-010 – summary of response rates (ITT population) based on best response assessments[40, 41]

	Study MM-009		Study MM-010	
	Len/Dex n=177	**Dex n=176**	**Len/Dex n=176**	**Dex n=175**
Response [a] [b]				
CR [c]	25 (14.1%)	1 (0.6%)	28 (15.9%)	6 (3.4%)
RR	52 (29.4%)	16 (9.1%)	46 (26.1%)	16 (9.1%)
PR	31 (17.5%)	18 (10.2%)	32 (18.2%)	20 (11.4%)
SD	54 (30.5%)	102 (58.0%)	53 (30.1%)	97 (55.4%)
PD	5 (2.8%)	25 (14.2%)	3 (1.7%)	25 (14.3%)
NE [d]	10 (5.6%)	14 (8.0%)	14 (8.0%)	11 (6.3%)
p-value [e]	<0.001		<0.001	
Dichotomised response				
CR, RR or PR	108 (61.0%)	35 (19.9%)	106 (60.2%)	42 (24.0%)
SD, PD or NE	69 (39.0%)	141 (80.1%)	70 (39.8%)	133 (76.0%)
p-value [f]	<0.001		<0.001	
Odds ratio [g] [95% CI]	6.31 [3.91, 10.17]		4.80 [3.03, 7.59]	

CI, confidence interval; CR, complete response; NE, not evaluable; PD, progressive disease, ; PR, partial response; RR, remission response, SD, stable disease.
[a] Response in this table is based on the review of all myeloma assessment data using Blade criteria.
[b] Response is the highest assessment of response during the treatment phase of the study.
[c] Comparison of the CR rate shows that the CR rate is significantly higher in the Len/Dex group than in the placebo/Dex group (p<0.003 continuity corrected Pearson chi square).
[d] Including subjects who did not have any response assessment data at the data cut-off point, or whose only assessment was 'response not evaluable'.
[e] Probability from Wilcoxon rank sum test.
[f] Probability from continuity-corrected Pearson chi square test.
[g] Calculated based upon the reported response rates
The median follow-up was 17.6 months for MM-009 and 16.4 months for MM-010.

Evidence for Len/Dex after one prior therapy

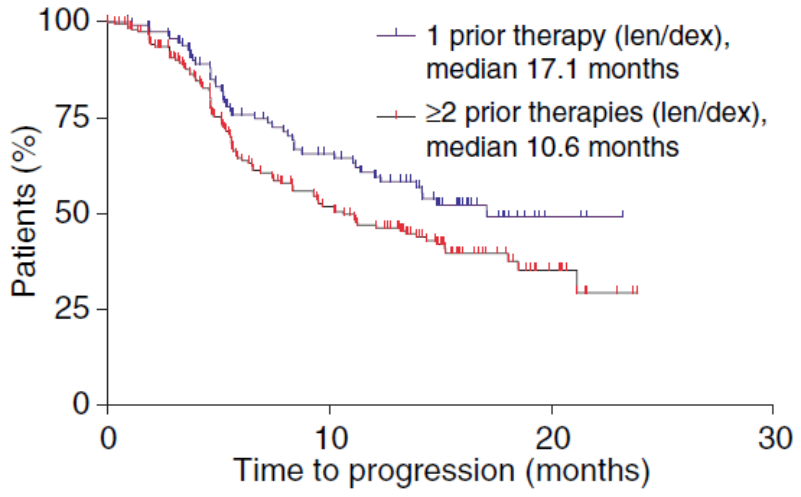
Subgroup analyses of pooled efficacy data from studies MM-009 and MM-010

Stadtmauer et al conducted a subset analysis of data from Studies MM-009 and MM-010, which compared the efficacy of Len/Dex at first relapse with its use as a later therapy in relapsed or refractory multiple myeloma. This analysis encompassed 353 Len/Dex patients, of whom 133 had received one prior therapy and 220 had received two or more prior therapies.[5]

Time to progression results

Analysis of data up to unblinding from studies MM-009 and MM-010 revealed that Len/Dex-treated patients who had received one prior therapy had a significantly longer TTP than patients who had received two or more prior therapies (17.1 months versus 10.6 months [HR 0.68, 95% CI 0.48–0.97]; p=0.026) (Figure 13).

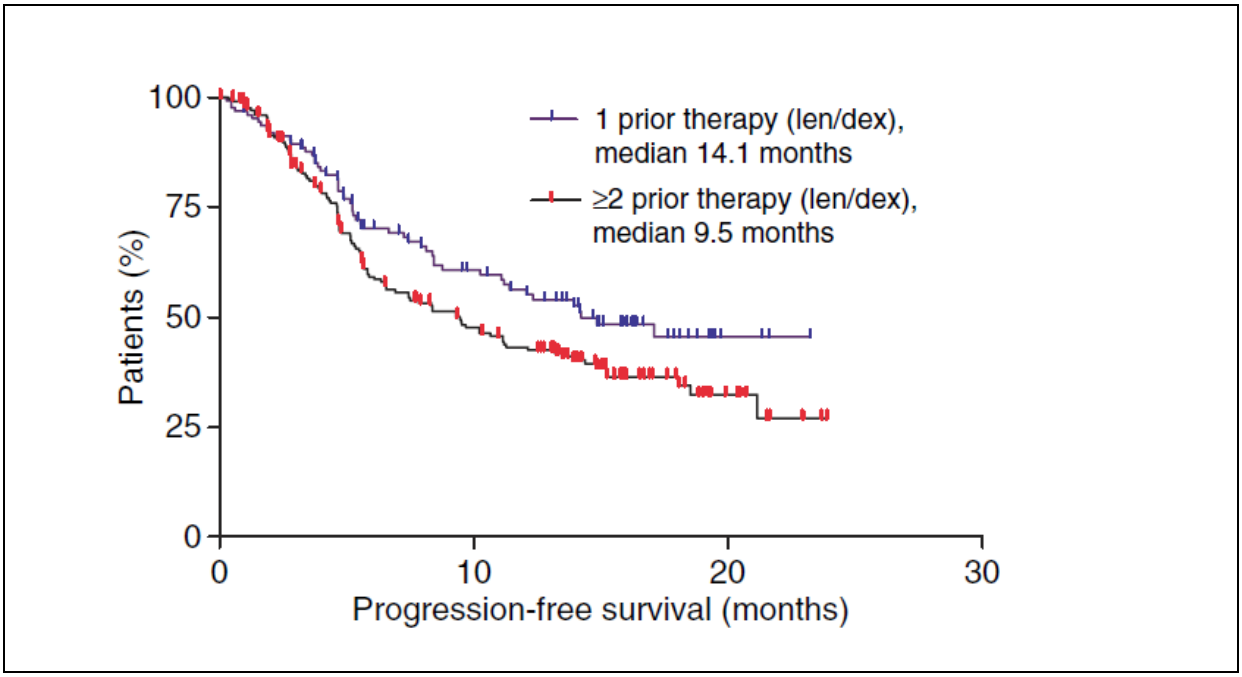
Figure 13: Kaplan–Meier estimates of TTP of patients treated with Len/Dex by number of prior therapies[5]



Progression-free survival results

PFS was also significantly longer in Len/Dex-treated patients who had received one prior therapy than those treated with two or more prior lines of therapy (median of 14.1 months versus 9.5 months [HR 0.71, 95% CI 0.2–0.99]; p=0.047) (Figure 14).

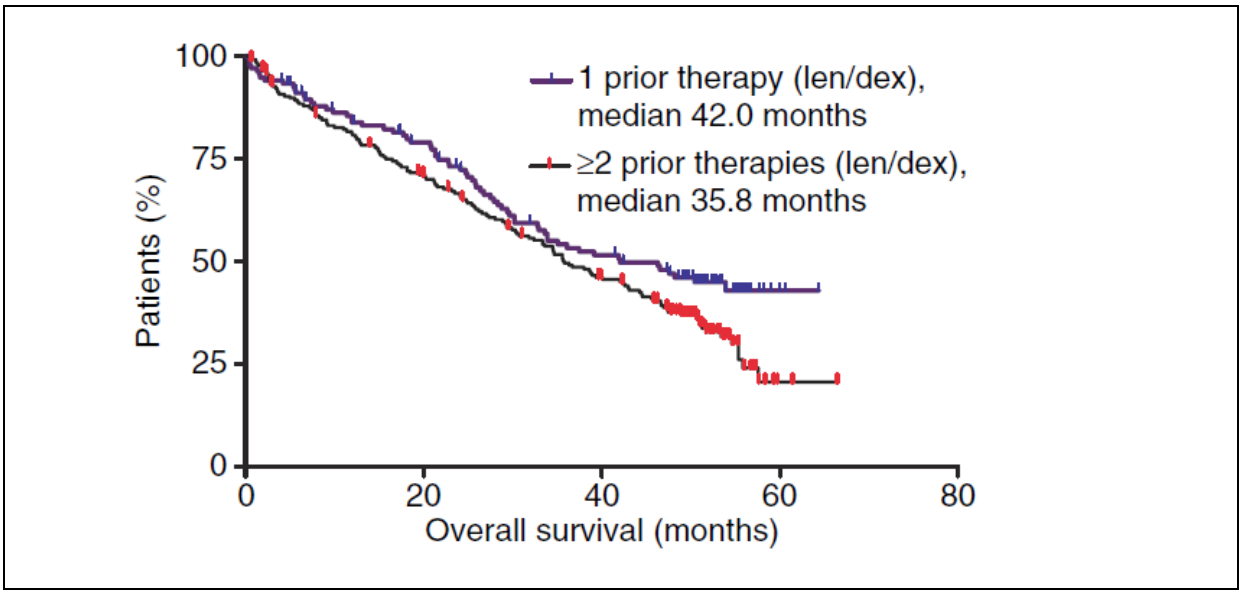
Figure 14: Kaplan–Meier estimates of PFS of patients treated with Len/Dex by number of prior therapies[5]



Overall survival results

OS from study enrolment was significantly longer in Len/Dex patients treated with one prior therapy than in those who had received two or more prior lines of therapy (median OS of 42.0 versus 35.8 months; p=0.041) (Figure 15).

Figure 15: Kaplan–Meier estimates of OS of patients treated with Len/Dex by number of prior therapies[5]



Response results and other outcomes

Treatment response and other outcomes of Len/Dex-treated patients with one prior therapy versus those with two or more prior therapies are presented in Table 21.

Table 21: Outcomes in patients by number of prior therapies[5]

	Len/Dex		
	1 prior therapy (n=133)	**≥2 prior therapies (n=220)**	**p-value**
Response rates, n (%)			
Overall response	89 (66.9)	125 (56.8)	0.060
CR	27 (20.3)	26 (11.8)	0.028
VGPR	26 (19.5)	35 (15.9)	
CR + VGPR	53 (39.8)	61 (27.7)	0.025
Partial response	36 (27.1)	64 (29.1)	
Stable disease	30 (22.6)	77 (35.0)	
Progressive disease	6 (4.5)	2 (0.9)	
Response not evaluable	8 (6.0)	16 (7.3)	
Median duration of treatment, months (range)	12.5 (0.3–24.1)	9.2 (0.03–24.8)	<0.001
Median duration of response, months (range)	NR (11.4–NR)	13.0 (8.4–NR)	0.21
Patients who relapsed, %	34.5	44.4	0.16
Patients who had a dose reduction [a], %	33.1	38.0	0.36
Patients who discontinued due to toxicity, %	14.3	14.5	0.54

[a] With or without interruption in lenalidomide treatment.
CR, complete response; NR, not reached; VGPR, very good partial response.

There was a trend towards a higher overall response to Len/Dex in patients with one prior therapy than in those with at least two prior therapies (66.9% versus 56.8%; p=0.06). However, a CR or a VGPR to Len/Dex was achieved by more patients with one prior therapy than those with two or more prior therapies (39.8% versus 27.7%; p=0.025).

The median follow-up for Len/Dex responders was 15.5 months. The median duration of response to Len/Dex had not been reached in the cohort of patients with one prior therapy, whereas those with two or more prior therapies had a median duration of response of 13.0 months (p=0.21). Fewer Len/Dex responders with one prior therapy relapsed compared with those with two or more prior therapies (38.2% versus 45.6%) at the time of study unblinding.[5]

Subsequent pooled analysis by Dimopoulos et al demonstrated that the type of previous therapy did not affect response rates to treatment with Len/Dex.[44]

Subgroup analysis of efficacy data from studies MM-009 and MM-010: overall survival and progression-free survival in second-line patients only

A patient-level analysis of data from studies MM-009 and MM-010 was undertaken to evaluate OS and PFS in second-line patients only.[100] This analysis did not include TTP as this was not an outcome in the final scope agreed with NICE.

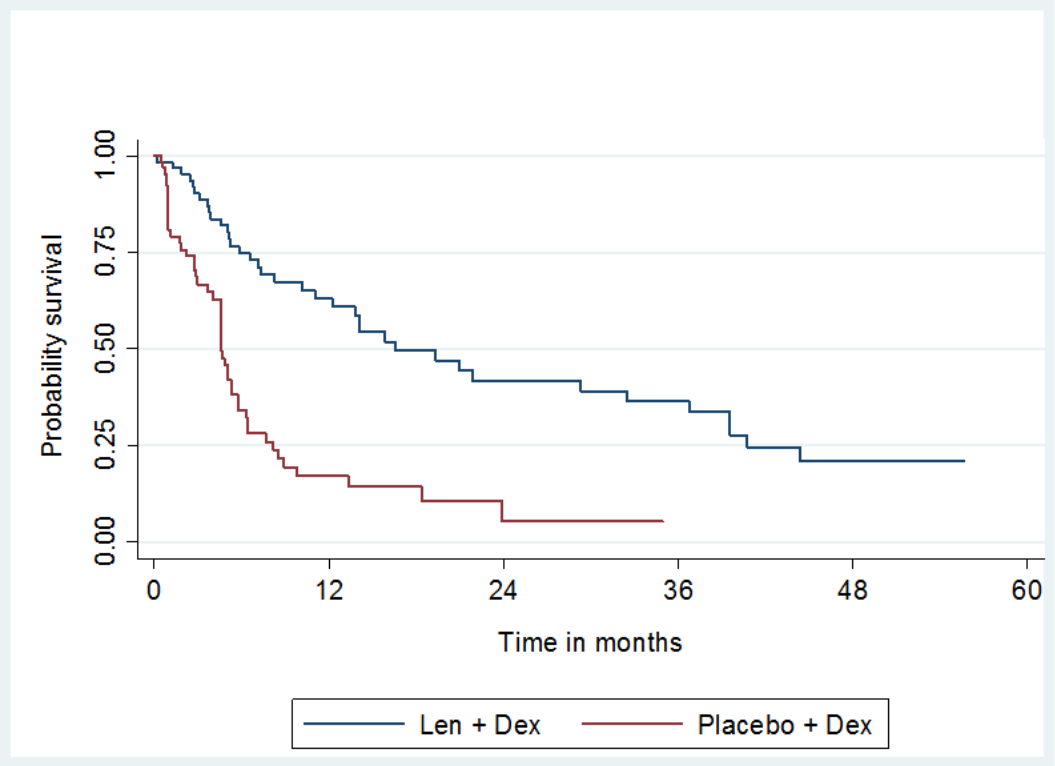
PFS results

Among second-line patients who participated in study MM-009, median PFS was longer in the Len/Dex group (16.6 months, 95% CI 11–36.8 months) than in the placebo/Dex group (4.6 months, 95% CI 4.0–5.7 months); this difference was statistically significant (HR 0.3, 95% CI 0.19–0.47; p<0.0001), Table 22 and Figure 16. Similarly, second-line patients from study MM-010 had longer median PFS with Len/Dex (13.3 months, 95% CI 5.1–26.9 months) than with placebo/Dex (4.5 months, 95% CI 2.8–5.6 months); again, this difference was statistically significant (HR 0.39, 95% CI 0.24–0.62; p<0.0001), see Table 22 and Figure 17. Notably, PFS rates of second-line patients from study MM-009 were comparable with those from study MM-010.[100]

Table 22: PFS of second-line patients in studies MM-009 and MM-010[100]

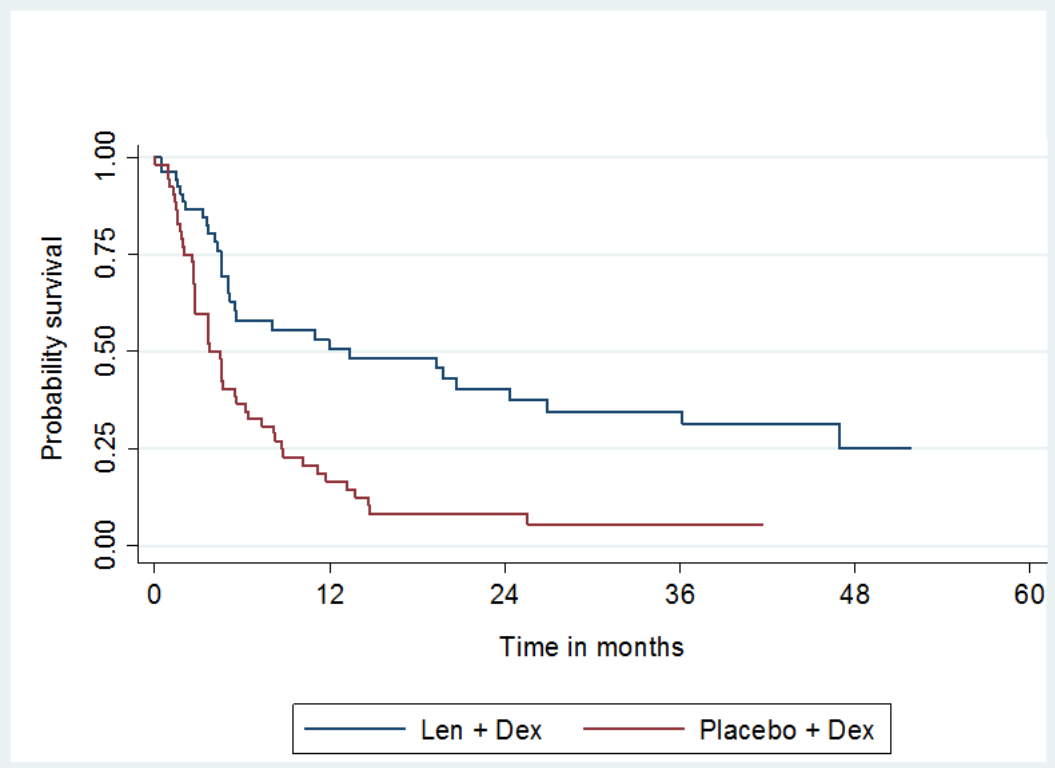
		Study MM-009		Study MM-010	
		Len/Dex	Dex	Len/Dex	Dex
PFS	n	68	67	56	57
Died	n (%)	37 (54.4)	48 (71.6)	31 (55.4)	48 (84.2)
Censored	n (%)	31 (45.6)	19 (28.4)	25 (44.6)	9 (15.8)
	Median (months)	16.6	4.6	13.3	4.5
	[95% CI]	[11.0, 36.8]	[4.0, 5.7]	[5.1, 26.9]	[2.8, 5.6]
Hazard ratio [95% CI]		0.30 [0.19, 0.47]		0.39 [0.24, 0.62]	
Log-rank test p-value		<0.0001		<0.0001	
PFS, progression-free survival.					

Figure 16: Kaplan–Meier estimates of PFS among second-line patients in study MM-009[100]



PFS, progression-free survival.

Figure 17: Kaplan–Meier estimates of PFS among second-line patients in study MM-010[100]



Progression-free survival.

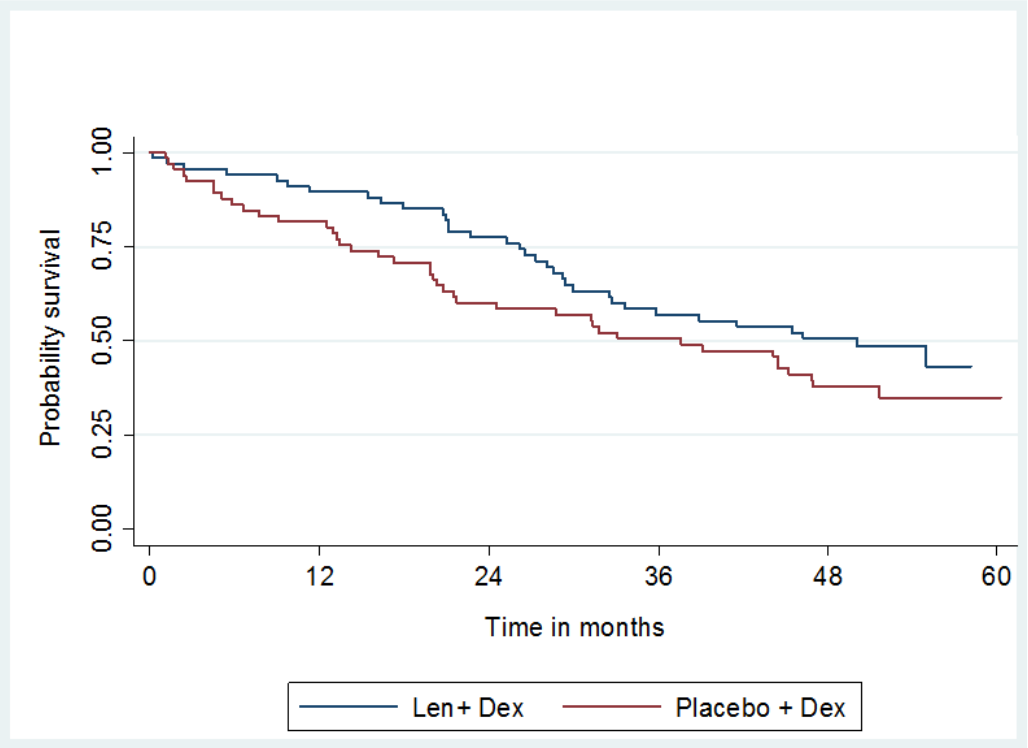
OS results

Among second-line patients who participated in study MM-009, median OS was numerically higher in the Len/Dex group (50.1 months, 95% CI 8.3–32.5 months) than in the placebo/Dex group (37.6 months, 95% CI 6.5–21.5 months), see Table 23 and Figure 18; however, this difference was not statistically significant (HR 0.70, 95% CI 0.44–1.10; p=0.1179). Among second-line patients from study MM-010, median OS was not reached in the Len/Dex group (not estimable [NE], 95% CI 34.3 months–NE), compared with 37.2 months (95% CI 2.1–23.5 months) in the placebo/Dex group, see Table 23 and Figure 19; again there was no significant difference between the two treatment groups (HR 0.71, 95% CI 0.41–1.23; p=0.2175).[100]

Table 23: OS of second-line patients in studies MM-009 and MM-010[100]

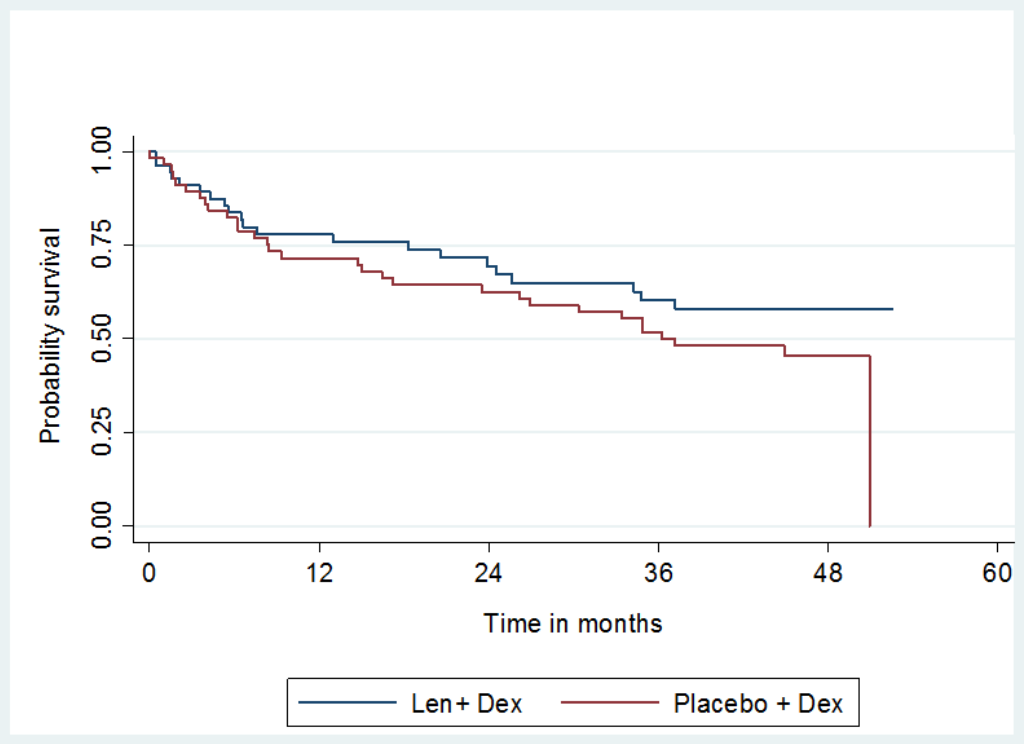
		Study MM-009		Study MM-010	
		Len/Dex	**Dex**	**Len/Dex**	**Dex**
OS	n	68	67	56	57
Died	n (%)	34 (50.0)	41 (61.2)	21 (37.5)	31 (54.4)
Censored	n (%)	34 (50.0)	26 (38.8)	35 (62.5)	26 (45.6)
	Median (months)	50.1	37.6	NE	37.2
	[95% CI]	[8.3, 32.5]	[6.5, 21.5]	[34.3, NE]	[2.1, 23.5]
Hazard ratio [95% CI]		0.70 [0.44, 1.10]		0.71 [0.41, 1.23]	
Log-rank test p-value		0.1179		0.2175	
CI, confidence interval; OS, overall survival; NE, not estimable.					

Figure 18: Kaplan–Meier estimates of OS among second-line patients in study MM-009[100]



OS, overall survival.

Figure 19: Kaplan–Meier estimates of OS among second-line patients in study MM-010[100]



OS, overall survival.

Health-related quality of life outcomes

Time to first worsening of ECOG-PS

The median time to first worsening of ECOG-PS was significantly greater in the Len/Dex arm of MM-009 versus placebo/Dex, while there was no significant difference between the two treatment arms of MM-010 with respect to this outcome (Table 24).[2]

Table 24: Studies MM-009 and MM-010 – time-to-first worsening of ECOG-PS (ITT population)[2]

		Study MM-009		Study MM-010	
	Statistic	**Len/Dex N=177**	**Dex N=176**	**Len/Dex N=176**	**Dex N=175**
Time to first worsening	N				
	n (%)	171	174	173	172
Worsened	n (%)	88 (51.5)	101 (58.0)	111 (64.2)	97 (56.4)
Censored		83 (48.5)	73 (42.0)	62 (35.8)	75 (43.6)
Overall time to first worsening (wk)	Median [95% CI]	36.3 [16.1, NE]	12.1 [8.3, 16.4]	10.1 [8.1, 16.1]	12.3 [10.1, 24.1]
	Mean	30.6	15.2	20.6	17.9
	SD	31.11	17.25	23.36	18.13
	Min, Max	0.0, 104.3	0.0, 80.9	0.0, 93.0	0.0, 88.4
Hazard ratio [95% CI]		1.448 [1.083, 1.937]		0.858 [0.653, 1.128]	
Log-rank Test p-value		0.012		0.271	

CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; NE, not estimable.

The median time to first worsening of ECOG-PS score was 36.3 weeks for Len/Dex-treated subjects in the MM-009 study and only 10.1 weeks in the Len/Dex-treated subjects in the MM-010 study. No differences in demographic features, safety profiles, or efficacy outcomes between the Len/Dex treatment groups of these two studies are evident to explain this difference in median time to ECOG-PS score worsening. In addition, while overall the MM-010 subjects had a shorter median time to ECOG-PS worsening, a smaller proportion of Len/Dex-treated MM-010 subjects than MM-009 subjects discontinued the study due to an adverse event.

It is likely that the discrepant result is due to a subjective difference in the assessment of ECOG-PS by the respective study investigators – as evidenced by the fact that a different pattern of ECOG-PS scoring in the total subject population was observed between the investigators of MM-010 and MM-009. This difference was not reflected in different objective efficacy or safety outcomes between the studies.

Time to first skeletal-related event

Regarding the 'time to first skeletal-related event' endpoint, there were too few events for both studies and no analysis could be performed.

Efficacy conclusions

Len/Dex doubles TTP and PFS versus placebo/Dex, in patients who have received at least one prior therapy for multiple myeloma. The combination of Len/Dex also increases response rates and ultimately survival when compared with placebo/Dex.

The evidence is derived from the two phase III placebo-controlled trials, MM-009 and MM-010, which included some 700 patients – representing a significant body of evidence, particularly given the orphan nature of the indication under investigation. Data for TTP, PFS, OS and response rates from study MM-009 were very similar to those from study MM-010.[86, 87]

These data are important, given the unmet need that is presented by multiple myeloma – being a highly debilitating and ultimately life-threatening haematological malignancy. The benefits afforded by lenalidomide plus dexamethasone are greatest in those patients who have received one, versus greater than one prior therapy. The increased survival afforded by this combination provides an important addition to the treatment armamentarium.

Results from a pooled analysis of data from studies MM-009 and MM-010 trials, with a median extended follow-up of 48 months, confirmed significant response outcomes and OS benefit with Len/Dex in relapsed or refractory multiple myeloma. Moreover, these data demonstrated that this significant OS benefit was achieved despite nearly half of the patients in the control arm of the study receiving lenalidomide at the time of disease progression or study unblinding.[32] In addition, subset analysis of pooled data from studies MM-009 and MM-010 indicated that TTP, PFS and OS were significantly prolonged and quality of response was superior, when Len/Dex was administered at first relapse compared with its use later as therapy.[5] Additional analysis also indicated that the type of prior therapy did not affect the response to treatment with Len/Dex.[63]

A patient-level analysis of data for second-line patients only from studies MM-009 and MM-010 indicated that Len/Dex was clearly superior to placebo/Dex in terms of prolongation of median PFS; in this subpopulation PFS rates were comparable across the two studies. Moreover, median OS was numerically greater with Len/Dex, although the difference did not reach statistical significance. [100] This is most likely due to the large number of patients crossing over from placebo/Dex to Len/Dex after unblinding.

Therefore, the additional analyses in the population that had received one prior therapy confirm that treatment with Len/Dex has a significant long-term clinical benefit in patients with relapsed or refractory multiple myeloma; and patients with fewer prior treatments will benefit more from Len/Dex treatment, making it a suitable second-line treatment option.

6.6 Meta-analysis

6.6.1 Follow the required steps when presenting a meta-analysis.

Not applicable

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Due to the primarily observational nature of the trials identified for comparator treatments, the inconsistency of the reporting of results, the poor level of reporting of baseline characteristics and small sample sizes a meta-analysis has not been conducted. Also, as no common comparator is available between the studies and multiple studies are only available for bortezomib, the information provided by a meta-analysis would be limited solely to the length of OS and PFS experienced by patients treated with bortezomib, with no comparative efficacy estimates possible based upon available data. As such the available trials are evaluated qualitatively (appendix C) and the quantitative impact of using alternative estimates of OS and PFS is assessed within the cost-effectiveness analysis (see section 7.3.2).

6.6.3 If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

Not applicable

6.7 Indirect and mixed treatment comparisons

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

It was not possible to conduct a mixed treatment comparison as all of the evidence identified for the comparators listed in the scope came from single arms of trials. No common comparator was presented that would allow an MTC to be conducted.

6.8 Non-RCT evidence

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results.

Quality assessment of relevant non-RCTs

Owing to an absence of head-to-head studies for Len/Dex and its comparators and studies with common comparators, the search strategy was widened to the individual comparators. The systematic review eligibility criteria were inclusive of both RCT and non-RCT study designs; the only excluded study design being that of single case studies. The details of the systematic review search strategy, search results screening and study selection criteria relevant to the identification of lenalidomide and comparator non-RCT evidence are described below (and in appendix C and sections 10.6 and 10.7, appendices 6 and 7).

Summary of methodology of relevant non-RCTs

The number of non-RCTs identified is summarised below according to the different interventions shown in Table 25.

Table 25: Number of studies identified

Intervention/comparators	Primary publication (n)	Secondary publication (n)
Lenalidomide plus dexamethasone	14	-
Bendamustine	1	-
Bortezomib treatment (monotherapy ± plus dexamethasone)	6	-
Cyclophosphamide plus other regimen	4	-
Doxorubicin plus other regimen	8	-
Melphalan plus other regimen	7	1
Vincristine	0	-

Summary of results of relevant non-RCTs

Len/Dex

14 studies were identified, the majority of which were single-centre, single-arm studies. Evidence from the 14 non- RCTs (Table 26) suggests Len/Dex is an effective treatment regimen for patients with relapsed or refractory multiple myeloma with ORR of above 60% reached in most cases. Prior treatment with bortezomib did not affect response rates. For completeness these studies are presented in appendix C.

Table 26: Summary of non-RCT evidence for Len/Dex

Study	Patient population	Country	n	Response rate	Median OS	Median PFS
MM-021[47]	rrMM with ≥1 prior anti-MM therapy	China	199	47.6%	NR	8.3 months
Kneppers 2010[52]	rrMM with ≥1 prior anti-MM therapy	Netherlands	114	69.3%	22 months	10 months
GEM-PETHEMA[56]	rrMM with ≥1 prior anti-MM therapy and progressive disease after ≥2 cycles of prior treatment	Spain	111	66.0%	17.4 months	NR
MM-018[56]	rrMM with ≥1 prior anti-MM therapy and no other therapeutic options available	Spain	63	78%	Not reached	13.3 months
Guglielmelli 2011[57]	rrMM with ≥1 prior anti-MM therapy including thalidomide	Italy	106	57.5%	17.4 months	10.5 months
Delforge 2011[60]	rrMM with ≥1 prior anti-MM therapy	Belgium	98	78% for patients previously responding to bortezomib 75% in patients unresponsive to bortezomib	NR	NR
Schwamborn 2011[84]	rrMM with ≥1 prior anti-MM therapy and unable to be treated with the usual dose of lenalidomide	Germany	10	80%	Not reached	4 months
Klein 2011[62]	rrMM with ≥1 prior anti-MM therapy and renal impairment	Germany	167	61.7%	25.8 months	NR
Dimopoulos 2012[63]*	rrMM with ≥1 prior anti-MM therapy and impaired renal function	Greece	102	64% for mild or no RI 56% for moderate RI 50% for severe RI	38.9 months for mild or no RI 29.0 months for moderate RI 18.4 months for severe RI	11.1 months for mild or no RI 9.5 months for moderate RI 7.8 months for severe RI
Moscetti 2012[65]	rrMM with ≥1 prior anti-MM therapy	Italy	33	53.5%	NR	14 months
Oehrlein 2012[66]	rrMM with ≥1 prior anti-MM therapy	Germany	67	82.1%	33.2 months	NR
Touzeau	rrMM with ≥1 prior anti-MM therapy and	France	45	62%	Not reached	14 months

Study	Patient population	Country	n	Response rate	Median OS	Median PFS
2012[69]	age ≥75					
Iida 2010[79]	rrMM with ≥1 prior anti-MM therapy	Japan	6	100%	NR	NR
Dimopoulos 2010b[81]	rrMM with ≥1 prior anti-MM therapy	Greece	50	71%	16 months	9 months
MM, multiple myeloma; OS, overall survival; NR, not reported; PFS, progression-free survival; RI, renal impairment; rrMM, relapsed or refractory multiple myeloma. * results reported for low-dose dexamethasone group						

Bortezomib

Six studies were identified, the majority of which were multicentre, single-arm studies. Evidence from the 6 non-RCTs with bortezomib suggests has a lower response rate than lenalidomide (20-65%), with response being dependent upon initial response to bortezomib (higher probability of response for patients who responded initially). Results are presented in Table 27.

The study reported by Taverna et al is the most relevant. It is used for economic modelling (section 7) because it was the only study measuring OS conducted in a European population where 100% of patients had previously been treated with bortezomib.[45] A fuller description of this study is therefore presented below. For completeness the remaining studies are presented in appendix C.

Table 27: Summary of non-RCT evidence for bortezomib

Study	Patient population	Country	n	% received prior bortezomib	Response rate	Median OS	Median PFS
RETRIEVE[53]	rrMM with ≥1 prior anti-MM therapy & at least a partial response to prior bortezomib-based therapy	Europe	130	100%	40%	NR	NR
Hruovsky 2010[50]	rrMM with ≥1 prior anti-MM therapy & response to prior bortezomib-based therapy	Germany and Switzerland	60	100%	63.3%	NR	9.3 months
Conner 2008[51]	rrMM with ≥1 prior anti-MM therapy & ≥4 prior bortezomib doses	USA	82	100%	21%	NR	NR
Sood 2009[61]	rrMM with ≥1 prior anti-MM therapy & response to prior bortezomib-based therapy	USA, Canada	32	100%	50%	NR	NR
ECOG E2A02*[80]	High risk MM & one prior therapy with bortezomib	USA	42 (n=7 retreatment)	7 of 42	28.6%	NR	7.9 months
Taverna 2012[45]	rrMM with ≥ 1 prior anti-MM therapy & response to prior bortezomib-based therapy	Switzerland	42	100%	64.3%	20.4 months	10.5 months

MM, multiple myeloma; OS, overall survival; NR, not reported; PFS, progression-free survival; rrMM, relapsed or refractory multiple myeloma.
*results reported for the 7 patients receiving retreatment.

Taverna et al, 2012 – study summary[45]

Overview

A retrospective survey was conducted across 26 centres in Switzerland, involving relapsed multiple myeloma patients who had responded to initial bortezomib therapy, presented with progressive or relapsed disease and were subsequently retreated with bortezomib (1.0 or 1.3mg/m^2 IV) after a treatment-free interval (TFI). The first TFI was the time between the end of prior bortezomib treatment and the start of bortezomib retreatment (or start of multiple myeloma-specific interim treatment); the second TFI was the time between the end of bortezomib retreatment and the start of next therapy after bortezomib retreatment. In total, 43 patients were enrolled (safety population) and 42 were evaluated for response (per protocol population). Inclusion criteria comprised patients with relapsed multiple myeloma aged ≥18 years, previous treatment with bortezomib therapy resulting in CR, nCR or PR, and a completed retreatment regimen with bortezomib after relapse or disease progression. The study also recorded details of any other multiple myeloma-specific therapy administered to study participants between the two courses of bortezomib treatment.[45]

Results

Patient characteristics

The median patient age at the start of bortezomib retreatment was 63 years. Patients had received a median of 2 prior multiple myeloma therapies (range 1–11 therapies) before bortezomib retreatment, with the most common being vincristine-adriamycin-dexamethasone (54.8%), thalidomide-dexamethasone (50%) and melphalan-prednisone (33%). Moreover, 31% of patients had undergone prior stem cell transplantation.[45]

Initial bortezomib treatment and response

Patients in the per-protocol population received a median of 4 cycles of bortezomib (range 2–19 cycles) as the initial treatment, with the majority (83.3%) having received 1–6 cycles. Fifty percent of patients received concomitant dexamethasone with their initial bortezomib treatment. All patients had achieved PR or better with initial bortezomib therapy, with 33.3% attaining CR or nCR. The median time to response with initial bortezomib treatment was 2.4 months (range 0.7–6.4 months). The median first treatment-free interval was 8.9 months (range 0.3–39.0 months),

the median duration of first response after initial bortezomib therapy was 7.3 months (range 0–37.7 months), and median TTP was 10.7 months (range 2.7–54.4 months) for the first progression. [45]

Interim anti-multiple myeloma therapy

A total of 12 patients (28.6%) received multiple myeloma-specific interim therapy between initial bortezomib treatment and retreatment. Interim therapies, either as monotherapy or in combination, included dexamethasone (n=5), thalidomide or lenalidomide (n=4) and autologous stem cell transplantation (n=2). [45]

Bortezomib retreatment

Patients had received a median of 2 therapies (range 1–11 therapies) prior to bortezomib retreatment. Bortezomib retreatment consisted of a median of 3 cycles (range 1–19), with 90.4% patients receiving 1–6 cycles. At retreatment, 27 patients (64.3%) took concomitant dexamethasone, while 20 patients (47.6%) were administered other concomitant medications, including 6 patients (14.3%) who received concomitant anti-neoplastic or immunomodulating agents. [45]

Bortezomib retreatment had an overall response rate (CR + nCR + PR) of 64.3% and a clinical benefit rate (CR + nCR + PR + stable disease) of 83%. In total, 85.7% of patients who attained CR or nCR with initial bortezomib treatment also attained CR or nCR with retreatment. Among the subgroup of patients with a first TFI of >6 months, response rate to bortezomib retreatment was higher than in those with a first TFI of ≤6 months (74.1% versus 46.7%; p=0.10). Moreover, response rate was lower in patients who received concomitant dexamethasone than in those who did not (57.1% versus 78.6%: p=0.31). The median duration of response following bortezomib retreatment was 12.6 months (range 0–37.7 months), with 35% (95% CI 20.6–51.7) of patients still responders at data cut-off. Median TTP following bortezomib retreatment was 10.5 months (range 0.4–≥39.5 months).

Median OS from first diagnosis, after prior bortezomib and after bortezomib retreatment was 9.3, 3.5 and 1.7 years, respectively. At the time of data cut-off following bortezomib retreatment, 14 patients had died, 4 had progressive disease as best response, 4 had stable disease, 5 had PR and 1 had CR.

Safety

Bortezomib as retreatment was well tolerated, and the safety profile was consistent with previous studies of bortezomib in relapsed multiple myeloma. The most common adverse drug reactions attributed to bortezomib were nervous system disorders (including peripheral neuropathy) and blood/lymphatic system disorders, which were reported by 5 and 3 patients, respectively. Bortezomib was discontinued in 6 patients due to: peripheral neuropathy (n = 2), lung infection (n=1), unknown drug toxicity and peripheral neuropathy (n=1), abdominal pain and nausea (n=1), and thrombocytopenia (n=1). All adverse drug reactions except peripheral neuropathy had resolved at the time of data analysis. A total of 6 patients reported a total of 9 suspected serious adverse events; 3 patients discontinued bortezomib treatment. Serious adverse drug reactions in the 3 patients who remained on bortezomib retreatment were peripheral neuropathy, neutropenia and asthenia (n=1), thrombocytopenia (n=1), and cardiovascular disorder (n=1).[45]

Bendamustine

One study was identified for bendamustine and is summarised below.

Damaj et al, 2012 –study summary[46]

Overview

A retrospective study in France collected data for 110 patients with relapsed or refractory multiple myeloma following prior treatment (which had to include alkylators, steroids, IMiDs and bortezomib). Patients were participating in a compassionate use programme in which they received treatment with bendamustine. Per protocol, the dose of bendamustine was 120–150mg/m^2 IV, in combination with prednisone, on days 1 and 2 of 28-day treatment cycles; however dose modification was at the physicians' discretion. The aims of the study were to evaluate the response rate to bendamustine, the duration of response, PFS and OS. Response rates were assessed according to EBMT criteria, OS was calculated from the first dose of bendamustine and PFS included death from any cause or progression as events.[46]

Results

Patient characteristics

The median patient age at the start of bendamustine treatment was 63 years (range 34–83 years). Patients had received a median of 4 prior multiple myeloma therapies (range 1–9 therapies). All 110 patients had previously received treatment with steroids, alkylators, bortezomib and IMiDs (either lenalidomide or thalidomide); 66 patients had undergone prior autologous stem cell transplantation.[46]

Bendamustine treatment

Among 90 patients for whom disease status could be evaluated at the time of their first bendamustine dose, 71 had progressive disease following their last multiple myeloma treatment. The median time from multiple myeloma diagnosis to bendamustine treatment was 60 months (range 10–224 months), and the median time from most recent prior therapy to bendamustine treatment was 10 days (range 0–496 days). A median of 4 cycles (range 1–13 cycles) of bendamustine were administered. The initial bendamustine dose ranged from 60–150mg/m^2 per day on days 1 and 2 of a 28-day cycle; dose of concomitant steroids was also variable. Overall, 31 patients received more than 6 cycles and 38 patients had fewer than 3 cycles of bendamustine.[46]

The overall response rate (≥PR) to bendamustine treatment was achieved by 33 patients (30%), including 2 patients (2%) with CR; 22 patients (20%) had stable disease, while 55 patients (50%) did not respond to bendamustine. Notably, 30 patients (27%) refractory to lenalidomide and 33 patients (31%) refractory to thalidomide and bortezomib were found to respond to bendamustine. After a median follow-up of 10 months, 49 patients had died due to progression or other causes related to myeloma and 61 patients were still alive. Of the living patients, 2 had attained CR, 27 had achieved PR, 15 had stable disease and 16 had progressive disease. At data cut-off, median duration of response had not been reached. Moreover, 66% of patients responding to bendamustine therapy remained in response more than 6 months after initiation of bendamustine therapy.

Overall, following bendamustine treatment, median PFS was 9.3 months and median OS was 12.4 months.

Safety

Evaluation of the toxicity of the drug was not one of the objectives of this study trial, and therefore adverse event data were not retrospectively collected.[46]

Chemotherapies

All evidence identified for treatment with chemotherapy related included combination with either bortezomib or lenalidomide and is therefore not reported in this section (see appendix C for details).

6.9 Adverse events

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (*www.york.ac.uk/inst/crd*). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

None of the relevant RCTs had safety as a primary objective

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

Key safety results

- Lenalidomide, in combination with dexamethasone, has a manageable tolerability profile. The most common adverse events ascribed to Len/Dex are haematological in nature – principally neutropenia and thrombocytopenia. Adverse events of this nature are familiar to, and well managed by, haemato-oncologists. The frequency of febrile neutropenia, was low illustrating that neutropenia can be effectively managed with monitoring and appropriate intervention, including dose reduction and dose interruption.[40, 41]

- Importantly, the clinical studies did not report any increase in the incidence of peripheral neuropathy for lenalidomide treated patients. This finding is in contrast to other agents used in the treatment of multiple myeloma where the increased occurrence of peripheral neuropathy can be treatment limiting.[40, 41]
- Pooled analysis of safety data from the MM-009 and MM-010 trials, with a median extended follow-up of 48 months, indicated that Len/Dex treatment remained well tolerated after long-term use.[32]
- Sub-analysis of pooled data from studies MM-009 and MM-010 showed that incidence of NCI-CTC grade 3 and 4 adverse events associated with Len/Dex was similar in patients with either one or at least two prior therapies, with neutropenia occurring most frequently.[5]
- Bortezomib retreatment has a management tolerability profile. The most common adverse events ascribed to bortezomib are also haematological in nature – principally neutropenia and thrombocytopenia. Gastro-intestinal adverse events (e.g. diarrhoea), anaemia and peripheral neuropathy are also relatively common.[42, 45, 50, 51, 53, 106]

Safety from studies MM-009 and MM-010

The discussion of comparative safety included here is taken from the scientific discussion produced as part of the European Public Assessment Report (EPAR) for lenalidomide, the SPC and the primary publications.[1, 2, 40, 41]

Additional pooled analysis, long-term data and expanded access program data are presented in appendix E.

The pooled safety database as of 31 December 2005 includes 703 patients (353 in the Len/Dex group and 350 in the placebo/Dex group) and shows the patient exposure as indicated below in Table 28. Median duration of treatment in the Len/Dex arm was 44.0 weeks, with 46.2% of patients completing at least 52 weeks of therapy.

Table 28: Pooled duration of treatment in studies MM-009 and MM-010[2]

	Len/Dex N=353		Dex N=350	
Treatment phase duration				
	N	**%**	**n**	**%**
<1 week	1	0.3	2	0.6
1 to <4 weeks	14	4.0	14	4.0
4 to <8 weeks	14	4.0	38	10.9
8 to 12 weeks	27	7.6	42	12.0
12 to <16 weeks	15	4.2	28	8.0
16 to <20 weeks	18	5.1	31	8.9
20 to <24 weeks	16	4.5	23	6.6
24 to <28 weeks	19	5.4	38	10.9
28 to <32 weeks	19	5.4	27	7.7
32 to <36 weeks	10	2.8	12	3.4
36 to <40 weeks	11	3.1	15	4.3
40 to <44 weeks	12	3.4	13	3.7
44 to <48 weeks	8	2.3	8	2.3
48 to <52 weeks	6	1.7	4	1.1
≥52 weeks	163	46.2	55	15.7
Duration of exposure (weeks)				
n	353		350	
Mean	53.9		29.7	
SD	38.76		26.41	
Median	44.0		23.1	
Min, Max	0.1, 161.7		0.3, 124.0	
Min, minimum value; Max, maximum value; SD, standard deviation.				

All grades of adverse events observed in at least 10% of patients

The safety population included those patients who had received at least one dose of study medication. Table 29 presents the pooled results of all adverse events that were reported by the patients or observed by the investigators and recorded in the case report form for Studies MM-009 and MM-010 (≥10% of cases). The severity of adverse events and laboratory abnormalities was graded according to NCI CTC Version 2.0.[96]

Table 29: Studies MM-009 and MM-010 – adverse events reported in at least 10% of patients in either treatment group[2]

MedDRA System Organ Class/ Preferred Term	Len/Dex (N=353) Grade 1-4 n (%)	Len/Dex (N=353) Grade 3–4 n (%)	Dex (N=350) Grade 1-4 n (%)	Dex (N=350) Grade 3-4 n (%)
Blood and Lymphatic System Disorders				
Neutropenia	152 (43.1)	125 (35.4)	23 (6.6)	12 (3.4)
Anaemia NOS	119 (33.7)	38 (10.8)	83 (23.7)	21 (6.0)
Thrombocytopenia	80 (22.7)	46 (13.0)	37 (10.6)	22 (6.3)
Eye Disorders				
Vision Blurred	60 (17.0)	1 (0.3)	40 (11.4)	1 (0.3)
Gastrointestinal Disorders				
Constipation	149 (42.2)	8 (2.3)	77 (21.7)	2 (0.6)
Diarrhoea NOS	137 (38.8)	11 (3.1)	98 (28.0)	4 (1.1)
Nausea	92 (26.1)	7 (2.0)	76 (21.7)	2 (0.6)
Dyspepsia	59 (16.7)	1 (0.3)	51 (14.6)	2 (0.6)
Vomiting NOS	42 (11.9)	4 (1.1)	32 (9.1)	4 (1.1)
Abdominal Pain NOS	37 (10.5)	5 (1.4)	22 (6.3)	1 (0.3)
General Disorders and Administration Site Conditions				
Fatigue	161 (45.6)	25 (6.5)	129 (37.4)	17 (4.9)
Asthenia	103 (29.2)	17 (4.8)	86 (24.9)	18 (5.1)
Pyrexia	100 (28.3)	5 (1.4)	67 (19.4)	12 (3.4)
Oedema Peripheral	95 (26.9)	6 (1.7)	65 (18.8)	4 (1.1)
Oedema NOS	37 (10.5)	3 (0.8)	33 (9.4)	2 (0.6)
Infections and Infestations				
Upper Respiratory Tract Infection NOS	87 (24.6)	5 (1.4)	55 (15.7)	2 (0.6)
Pneumonia NOS	49 (13.9)	32 (9.1)	30 (8.6)	19 (5.4)
Investigations				
Weight Decreased	68 (19.3)	3 (0.9)	53 (15.1)	1 (0.3)
Metabolism and Nutrition Disorders				
Hyperglycaemia NOS	57 (16.1)	27 (7.6)	50 (14.3)	27 (7.7)
Anorexia	57 (16.1)	2 (0.6)	36 (10.3)	3 (0.9)
Hypokalaemia	52 (14.7)	20 (5.7)	21 (6.0)	5 (1.4)
Musculoskeletal and Connective Tissue Disorders				
Muscle Cramp	121 (34.3)	3 (0.9)	76 (21.7)	1 (0.3)
Back Pain	91 (25.8)	6 (1.7)	67 (19.1)	6 (1.7)
Arthralgia	63 (17.8)	2 (0.6)	63 (18.0)	7 (2.0)
Muscle Weakness NOS	56 (16.0)	20 (5.7)	56 (16.0)	11 (3.1)
Bone Pain	51 (14.4)	8 (2.3)	40 (11.4)	5 (1.4)
Pain in Limb	41 (11.6)	1 (0.3)	33 (9.4)	5 (1.4)
Myalgia	37 (10.5)	4 (1.1)	38 (10.9)	2 (0.6)
Nervous System Disorders				
Headache	94 (26.6)	3 (0.8)	85 (24.3)	1 (0.3)
Dizziness	83 (23.5)	7 (2.0)	59 (16.9)	3 (0.9)
Tremor	75 (21.2)	2 (0.6)	26 (7.4)	4 (1.1)
Dysgeusia	54 (15.3)	0 (0)	34 (9.7)	0 (0)
Paraesthesia	51 (14.4)	1 (0.3)	47 (13.4)	0 (0)
Hypoesthesia	37 (10.5)	1 (0.3)	26 (7.4)	0 (0)
Psychiatric Disorders				
Insomnia	129 (36.5)	4 (1.1)	133 (38.0)	1 (0.3)
Depression	45 (12.7)	10 (2.8)	37 (10.6)	6 (1.7)

MedDRA System Organ Class/ Preferred Term	Len/Dex (N=353) Grade 1-4 n (%)	Len/Dex (N=353) Grade 3–4 n (%)	Dex (N=350) Grade 1-4 n (%)	Dex (N=350) Grade 3-4 n (%)
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	90 (25.5)	2 (0.6)	86 (24.6)	1 (0.3)
Dyspnoea NOS	85 (24.1)	10 (2.8)	60 (17.1)	10 (2.9)
Nasopharyngitis	65 (18.4)	2 (0.6)	31 (8.9)	0 (0)
Pharyngitis	53 (15.0)	0 (0)	34 (9.7)	0 (0)
Bronchitis NOS	41 (11.6)	2 (0.6)	30 (8.6)	5 (1.4)
Skin and Subcutaneous Tissue Disorders				
Rash NOS	76 (21.5)	2 (0.6)	35 (10.0)	0 (0)
Vascular Disorders – none ≥ 10% frequency				
NOS, not otherwise specified.				

Anaemia, neutropenia, thrombocytopenia, constipation, pneumonia, decreased weight, hypokalaemia, hypocalcaemia, tremor, rash, and deep vein thrombosis (DVT) were reported significantly more frequently in the Len/Dex group than in the placebo/Dex group. Neutropenia and thrombocytopenia were the primary reasons for dose reductions in the Len/Dex group.[2]

In common with many chemotherapeutic agents used in haematological malignancies and with which specialist haematologists and oncologists are familiar, myelosuppression was reversed by interruption of treatment, a reduction in dose or use of granulocyte-colony stimulating factor (G-CSF).[2]

The frequency of complications of neutropenia and thrombocytopenia such as infection and bleeding events were low and comparable between both groups. This further illustrates that neutropenia and thrombocytopenia can be effectively managed with monitoring and appropriate intervention, including dose reduction and dose interruption.[2]

Cardiac adverse events were more frequently reported in Len/Dex arm (18.1%) than in placebo/Dex arm (11.1%), particularly atrial fibrillation (4.2% including 3.1% serious) with Len/Dex and 1.1% with placebo/Dex (0.6% were serious). Of the 69 lenalidomide-treated patients experiencing cardiac adverse events (including irregular heart rate, cardiac murmur, decreased ejection fraction and abnormal ECG, Q wave, ST-T segment and prolonged QT), 56 were found to have had either an

underlying conditions or were taking concomitant medications (i.e., beta blocker, calcium channel blocker, anti-arrhythmic, etc.[2]

There were more reports of atrial fibrillation in the Len/Dex arm than the placebo/Dex arm. However, review of the 9 serious reports revealed that the majority of subjects had either a predisposing prior medical history or the event was reported in association with other events.

Serious events occurring in at least 1% of patients

Table 30 shows the serious adverse events, which were reported in at least 1% of patients. While neutropenia was among the most commonly reported events that occurred significantly more frequently in the Len/Dex arm, only 1.7% of patients were reported to have experienced febrile neutropenia.

Table 30: Studies MM-009 and MM-010 – serious adverse events reported in at least 1% of patients[2]

MedDRA System Organ Class/ Preferred Term	Len/Dex (N=353)		Dex (N=350)	
	n	%	n	%
Patients with at least one serious adverse event	202	57.2	163	46.6
Infections and Infestations	81	22.9	59	16.9
Pneumonia NOS	34	9.6	22	6.3
Respiratory Tract Infection NOS	4	1.1	7	2.0
Sepsis NOS	4	1.1	5	1.4
Upper Respiratory Tract Infection NOS	4	1.1	1	0.3
Urinary Tract Infection NOS	4	1.1	1	0.3
Vascular Disorders	40	11.3	20	5.7
Deep Vein Thrombosis	25	7.1	11	3.1
Hypotension NOS	2	0.6	4	1.1
General Disorders and Administration Site Conditions	29	8.2	20	5.7
Pyrexia	12	3.4	13	3.7
Metabolism and Nutrition Disorders	25	7.1	24	6.9
Dehydration	7	2.0	6	1.7
Hyperglycaemia NOS	5	1.4	6	1.7
Hypercalcaemia	1	0.3	6	1.7
Respiratory, Thoracic, and Mediastinal Disorders	25	7.1	22	6.3
Pulmonary Embolism	13	3.7	3	0.9
Nervous System Disorders	24	6.8	19	5.4
Cerebrovascular Accident	7	2.0	3	0.9
Gastrointestinal Disorders	22	6.2	19	5.4
Diarrhoea NOS	6	1.7	2	0.6
Abdominal Pain NOS	4	1.1	1	0.3
Renal and Urinary Disorders	17	4.8	17	4.9
Renal Failure NOS	6	1.7	9	2.6
Renal Failure Acute	5	1.4	4	1.1

MedDRA System Organ Class/ Preferred Term	Len/Dex (N=353)		Dex (N=350)	
	n	%	n	%
Cardiac Disorders	27	7.6	12	3.4
Atrial Fibrillation	11	3.1	2	0.6
Cardiac Failure Congestive	5	1.4	0	0
Pulmonary Oedema NOS	1	0.3	4	1.1
Blood and Lymphatic System Disorders	22	6.2	9	2.6
Febrile Neutropenia	6	1.7	0	0
Thrombocytopenia	5	1.4	5	1.4
Anaemia NOS	5	1.4	2	0.6
Neutropenia	5	1.4	1	0.3
Musculoskeletal and Connective Tissue Disorders	18	5.1	12	3.4
Bone Pain	4	1.1	0	0

NOS, not otherwise specified.

Cases of serious DVT and pulmonary embolism occurred more commonly in the Len/Dex and placebo/Dex arms (7.1% versus and 3.7% versus 0.9%, respectively; Table 30).

Deaths

As of 31 December 2005, 107 (30.3%) deaths had been reported among the 353 Len/Dex-treated patients and 142 (40.5%) deaths had been reported among the 351 placebo/Dex-treated patients. The primary cause of death in both treatment groups was disease progression (70/107 in the Len/Dex group and 101/142 in the placebo/Dex group).

Of the 107 deaths in the Len/Dex group, 24 were suspected by the investigators to be related to the study medication. Of the 142 deaths in the placebo/Dex group, 24 were suspected by the investigator to be related to the study medication.[2]

Dose reductions and interruptions

Table 31 summarises the information relating to dose reductions or interruptions across both studies.[101]

Table 31: Frequency of dose reductions or interruptions in Studies MM-009 and MM-010[101]

	Study MM-009				Study MM-010			
	Len/Dex		Dex		Len/Dex		Dex	
	n	%	n	%	N	%	n	%
At least one adverse event leading to dose reduction or interruption	113	66.5	91	53.5	125	71	83	47.4

Neutropenia and thrombocytopenia were the primary reasons for dose reductions in the Len/Dex groups, and the frequency of discontinuation was low – for MM-009, neutropenia (2.4%; 4/170) and thrombocytopenia (0.6%; 1/170) and for MM-010, neutropenia or thrombocytopenia (0.6% and 0.6%, respectively).

Peripheral neuropathy

Only a few cases suggesting a peripheral neuropathy are reported in the two phase III studies – MM-009 and MM-010 – and their incidence is comparable between Len/Dex and placebo/Dex groups (about 5 to 8% of drug-related peripheral sensory neuropathies/paraesthesia). MM-009 and MM-010 show no increase in the incidence of peripheral neuropathy in patients treated with lenalidomide.[1]

Thromboembolic events

There was a significant increased risk for developing thromboembolic adverse events (DVT, pulmonary embolism) in Len/Dex-treated patients compared with placebo/Dex- treated patients (9.1% versus 4.3% and 4.0% versus 0.9%, respectively). Risk factors have been identified as: concomitant erythropoietin treatment, a prior medical history of thrombosis, older age and lower baseline plasma cell count. In studies MM-009 and MM-010, all of the recorded cases of thrombosis reported with a rising paraprotein level at baseline.

Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone. Prophylactic antithrombotic medicines are recommended, especially in patients with additional thrombotic risk factors.[1]

Pooled analyses and long-term safety data from studies MM-009 and MM-010
Dimopoulos et al have published a pooled analysis of safety data from Studies MM-009 and MM-010, which also includes long-term findings.[32] This analysis encompassed 353 Len/Dex patients and 351 placebo/Dex patients.

The pooled safety analysis revealed that 83.3% of Len/Dex patients experienced at least one grade 3 or 4 AE, compared with 69.7% of patients who received placebo/Dex (p<0.0001); the nature of these are broken down in Table 32. Neutropenia and thrombocytopenia were the most common grade 3 or 4 adverse events among patients treated with Len/Dex and occurred significantly more frequently in those treated with placebo/Dex (p<0.001). Grade 3 or 4 hyperglycaemia was the most common event noted among placebo/Dex patients.

Table 32: Grade ≥3 adverse events occurring in more than 5% of patients[32]

Adverse event, n (%)	Len/Dex (n=353)	Dex (n=351)
Neutropenia	125 (35.4)**	12 (3.4)
Thrombocytopenia	46 (13.0)**	22 (6.3)
Anaemia	38 (10.8)*	21 (6.0)
Pneumonia	32 (9.1)	19 (5.4)
All thromboembolic events	56 (15.9)**	19 (5.4)
Hyperglycaemia	27 (7.6)	27 (7.7)
Fatigue	23 (6.5)	17 (4.9)
Muscle weakness	20 (5.7)	11 (3.1)
Hypokalaemia	20 (5.7)	5 (1.4)
Asthenia	17 (4.8)	18 (5.1)
* p<0.001; ** p<0.05.		

As previously reported, thromboembolic events were significantly higher in patients treated with Len/Dex in the absence of a prophylactic use of an anticoagulant (p<0.001). Grade 2 peripheral neuropathy was experienced by 1.4% of Len/Dex patients and 1.4% of placebo/Dex patients; grade 3 peripheral neuropathy occurred in 1.7% and 0.6% of the Len/Dex and placebo/Dex patients, respectively. There were no grade 4 peripheral neuropathic events in either group.

Subset analyses of pooled safety data from studies MM-009 and MM-010: Len/Dex given at first relapse versus later therapy
As part of the subset analysis of data from studies MM-009 and MM-010 conducted by Stadtmauer et al adverse events were also reported. The incidence of NCI-CTC grade 3 and 4 adverse events experienced by Len/Dex-treated patients who had

received one prior therapy versus two or more prior lines of therapy are presented in Table 33.

Table 33: Incidence of National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3 and 4 adverse events[5]

	Lenalidomide plus dexamethasone	
	1 prior therapy (n=133)	**≥2 prior therapies (n=220)**
Haematologic toxicities, n (%)		
Anaemia	13 (9.8)	25 (11.4)
Thrombocytopenia	12 (9.0)	34 (15.5)
Neutropenia	55 (41.4)	70 (31.8)
Infection	24 (18.0)	29 (13.2)
Febrile neutropenia	2 (1.6)	6 (2.6)
Non-haematologic toxicities, n (%)		
Deep-vein thrombosis／pulmonary embolism	14 (10.5)	27 (12.3)
Peripheral neuropathy	0 (0.0)	5 (2.3)
Fatigue	10 (7.5)	13 (5.9)
Gastrointestinal (nausea, vomiting, constipation)	8 (6.0)	7 (3.2)

In patients who had received one or two or more prior lines of therapy, the most common adverse event associated with Len/Dex was grade 3 and 4 neutropenia (41.4% and 31.8%, respectively). Moreover, incidence of febrile neutropenia was similar between Len/Dex-treated patients with one or two or more prior therapies (1.6% versus 2.6%; p=0.72). The most common grade 3 and 4 non-haematologic adverse events associated with Len/Dex in both cohorts were deep-vein thrombosis / pulmonary embolism, which occurred with comparable frequency (10.5 versus 12.3%, respectively; p=0.63). No grade 3 and 4 peripheral neuropathy was reported in Len/Dex-treated patients with one prior therapy.[5]

Additional safety considerations

In addition to the adverse events observed in clinical trials MM-009 and MM-010, there following safety considerations are also relevant for lenalidomide.

Elderly patients

The effects of age on the pharmacokinetics of lenalidomide have not been studied. Lenalidomide has been used in clinical trials in multiple myeloma patients up to 86 years of age. The percentage of patients aged 65 years or over was not significantly different between the Len/Dex and placebo/Dex groups. No overall difference in

safety or efficacy was observed between these patients and younger patients, but greater pre-disposition of older individuals cannot be ruled out. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

Use in patients with impaired renal function

Lenalidomide is substantially excreted by the kidney, therefore care should be taken in dose selection and monitoring of renal function is advised. No dose adjustments are required for patients with mild renal impairment.

The following dose adjustments are recommended at the start of therapy for patients with moderate or severe impaired renal function or end stage renal disease (Table 34).

Table 34: Dose adjustments in patients with impaired renal function[1]

Renal function (CLcr)	Dose adjustment
Moderate renal impairment (30≤CLcr <50mL/min)	10mg once daily*
Severe renal impairment (CLcr <30 mL/min, not requiring dialysis)	15mg every other day
End Stage Renal Disease (CLcr <30 mL/min, requiring dialysis)	5mg once daily. On dialysis days, the dose should be administered following dialysis.
CLcr, creatinine clearance. * The dose may be escalated to 15mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.	

Use in patients with impaired hepatic function

Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.[1]

Pregnancy warnings

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic substance that causes severe life-threatening birth defects. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide cannot be ruled out. For these reasons a risk minimisation plan was developed and agreed with the MHRA to ensure that there is no foetal exposure to lenalidomide.[107] The burden associated with implementation of this plan is minimal. The main objective of the plan is to inform of the potential teratogenic risk of lenalidomide and to restrict use in women of child-bearing potential, unless the pregnancy prevention programme is followed.[1]. Details of the programme are provided in appendix F.

Len/Dex safety conclusions

The data from MM-009 and MM-010 demonstrate that Len/Dex combination therapy is well tolerated in subjects with multiple myeloma who have received at least one prior therapy and that the addition of lenalidomide to dexamethasone is accomplished with a minimal increase in toxicity.[86, 87, 108]

The safety analysis highlighted a potential increased thrombotic risk in patients taking erythropoietic agents concomitantly with Len/Dex. In addition, neutropenia, thrombocytopenia, constipation, nausea, muscle cramp, tremor and dizziness were reported more frequently in the Len/Dex group than in the placebo/Dex group. Other adverse events were reported in comparable proportions of subjects in both treatment groups.

Moreover, results from a pooled analysis of safety data from the MM-009 and MM-010 trials, with a median extended follow-up of 48 months, indicated that Len/Dex treatment remained well tolerated after long-term use, with minimal increase in toxicity.[32]

In a sub-analysis of data from studies MM-009 and MM-010, incidence of NCI-CTC grade 3 and 4 adverse events associated with Len/Dex was similar in patients who had received one or two or more prior therapies, with neutropenia occurring most frequently, indicating that Len/Dex is tolerable for second-line multiple myeloma therapy.[5]

Lenalidomide is known to be excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. A dose-reduction regimen is recommended for patients with impaired renal function.

While lenalidomide is structurally related to thalidomide, the adverse event profile is distinct. Lenalidomide differs from thalidomide (currently an unlicensed drug in Europe) in that it is associated with a low incidence of grade 3 or 4 sedation, fatigue, rash, and in particular peripheral neuropathy.[40, 41, 109-111]

Bortezomib – non RCT evidence

The types of adverse events reported and whether these were all adverse events or only drug related adverse events varied by study (Table 35). The most commonly reported grade ≥3 adverse events were thrombocytopenia and neuropathy. Adverse events led to treatment discontinuation in 10–22% of patients.

Table 35: Summary of non-RCT adverse event evidence

Study	Patient population	Country	N	Grade ≥3 AEs	Treatment discontinuation due to AE	Most frequently reported grade ≥3 AEs
RETRIEVE[53]	rrMM with ≥ 1 prior anti-MM therapy & at least a partial response to prior bortezomib-based therapy	Europe	130	60%	13%	Thrombocytopenia (35%) Neutropenia (7%) Diarrhoea (7%) Pneumonia (6%) Anaemia (5%)
Hruovsky 2010[50]*	rrMM with ≥ 1 prior anti-MM therapy & response to prior bortezomib-based therapy	Germany and Switzerland	60	10.6%	10.6%	Thrombocytopenia (3%) Peripheral neuropathy (5%) Pyrexia (2%) Herpes zoster (2%) Anaemia (2%)
Conner 2008[51+]	rrMM with ≥ 1 prior anti-MM therapy & ≥ 4 prior bortezomib doses	USA	82	NR	22%	Neuropathy (6%) Fatigue (4%) Diarrhoea (2%) Dizziness (2%) Oedema (2%) Thrombocytopenia (2%)
Sood 2010[61]	rrMM with ≥ 1 prior anti-MM therapy & response to prior bortezomib-based therapy	USA, Canada	32	44%	NR	Congestive heart failure (3%)* Thrombocytopenia (3%)*
ECOG E2A02[80]	High risk MM & one prior therapy with bortezomib	USA	42 (n=7 retreatment)	NR	NR	NR
Taverna 2012[45]*	rrMM with ≥ 1 prior anti-MM therapy & response to prior bortezomib-based therapy	Switzerland	42	14%	14%	Nervous system disorders Including peripheral neuropathy (12%) Blood and lymphatic system disorders (7%) General disorders and administration site conditions (7%)

AEs, adverse events; MM, multiple myeloma; rrMM, relapsed or refractory multiple myeloma.
*adverse drug reactions reported rather than all adverse events +toxicities leading to discontinuation reported for most frequent adverse events.

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

In two phase III clinical trials (MM-009 and MM-010), the combination of lenalidomide and dexamethasone resulted in consistent and significant improvements in response rate, time to disease progression, and OS in relapsed or refractory patients compared to treatment with high-dose dexamethasone alone. Moreover, efficacy findings for PFS, TTP and response rates from study MM-009 were comparable with those from study MM-010.[40, 41] The results of these studies are notable given the prior treatment history of these patients and the severity of the disease.

The main efficacy results of these two double-blind randomised trials are as follows:

- The MM-009 and MM-010 clinical trials demonstrate that the addition of lenalidomide to dexamethasone significantly increases response rates, TTP, PFS and OS in patients with multiple myeloma following at least one prior therapy. The trials included 704 patients – representing a significant body of evidence, particularly given the orphan nature of the disease.[40, 41]
- The overall response rate seen in patients treated with Len/Dex was approximately three-fold higher than was seen with placebo/Dex (MM-009: 61.0% versus 19.9%, $p<0.001$) and (MM-010: 60.2% versus 24.0%, $p<0.001$).[40, 41]
- There was a statistically significant improvement in median TTP (the primary endpoint of the clinical studies) among patients enrolled in the Len/Dex arms, compared to the placebo/Dex arms of the two trials. In fact, median TTP was more than doubled with the combination treatment (MM-009: 11.1 versus 4.7 months, $p<0.001$) and (MM-010: 11.3 versus 4.7 months, $p<0.001$). [40, 41]

- In a pooled analysis of data from studies MM-009 and MM-010 trials, with a median extended follow-up of 48 months, 199 (56.4%) Len/Dex-treated patients had died, compared with 219 (62.4%) placebo/Dex-treated patients.OS was was significantly longer in patients treated with Len/Dex that those treated with placebo/Dex (median of 38.0 versus 31.6 months, respectively; p=0.045). This confirms the significant OS benefit of Len/Dex in relapsed or refractory multiple myeloma.[32]
- In addition, subset analysis of pooled data from studies MM-009 and MM-010 indicated that TTP (17.1 months versus 10.6 months; p=0.026), PFS (median of 14.1 months versus 9.5 months; p=0.047) and OS (42.0 versus 35.8 months; p=0.041) were significantly prolonged when Len/Dex was administered at first relapse compared with its use as a later therapy. This indicates that Len/Dex has a significant long-term clinical benefit in patients with relapsed or refractory multiple myeloma and patients who have received fewer prior treatments will get more benefit from treatment.[5]
- A patient-level analysis of data from both studies in second-line patients showed median PFS was longer in the Len/Dex group than in the placebo/Dex group (16.6 versus 4.6 months, p<0.0001) a numerically higher median OS in the Len/Dex group (50.1 months, 95% CI 8.3–32.5 months) compared to the placebo/Dex group (37.6 months, 95% CI 6.5–21.5 months.[100]

The main safety findings for lenalidomide can be summarised as follows:

- Lenalidomide, in combination with dexamethasone, has a manageable tolerability profile. The most common adverse events ascribed to lenalidomide are haematological in nature – principally neutropenia and thrombocytopenia. Adverse events of this nature are familiar to, and well managed by, haemato-oncologists. The frequency of febrile neutropenia, was low illustrating that neutropenia can be effectively managed with monitoring and appropriate intervention, including dose reduction and dose interruption.

- Importantly, the clinical studies did not report any increase in the incidence of peripheral neuropathy for lenalidomide treated patients. This finding is in contrast to other agents used in the treatment of multiple myeloma where the increased occurrence of peripheral neuropathy can be treatment limiting.
- Pooled analysis of safety data from the MM-009 and MM-010 trials, with a median extended follow-up of 48 months, indicated that Len/Dex treatment remained well tolerated after long-term use.[32] Furthermore, sub-analysis of data from studies MM-009 and MM-010 showed that the incidence of NCI-CTC grade 3 and 4 adverse events associated with Len/Dex was similar in patients who had received either one or at least two prior therapies, with neutropenia occurring most frequently. This indicates that Len/Dex is tolerable for second-line multiple myeloma therapy.[5]
- Owing to the structural similarities between lenalidomide and thalidomide, a risk management programme has been put place to reduce the risk of foetal exposure to lenalidomide. The programme employs a simple process that requires the physician and pharmacist to sign a prescription authorisation form highlighting compliance with the the risk minimisation plan.

Limited supporting evidence of efficacy and safety of lenalidomide when it is used at second line in the real-world setting is also available, see appendix E. Lenalidamide has been prescribed at second line for select patients through Individual funding requests (IFR) and more recently through the Cancer Drugs Fund (CDF) where patients have received initial treatment with bortezomib or are contra-indicated to the use of bortezomib.[4]

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Validity of the design of studies MM-009 and MM-010

Although there is no direct trial-based comparison of lenalidamide to the primary comparator treatments, the RCT data from MM-009 and MM-010

provide a body of well-controlled and robust data. In the context of this submission, these enable economic comparisons to be made against the limited non-RCT evidence identified.

Randomisation to the two treatment groups in a double-blind fashion minimises bias in the assessment of TTP and safety, and the multicentre design of the study provides reassurance that the results have general applicability to the population of subjects with multiple myeloma under investigation. The eligibility criteria require the subjects to have measurable disease to facilitate the accurate assessment of TTP (the primary efficacy endpoint). Randomisation was accomplished by a validated IVRS to ensure that registration and randomisation were performed quickly and conveniently. In order to maintain balance between the 2 treatment arms in the allocation of subjects with differing prognoses for TTP and survival, randomisation was stratified by the following prognostic features: baseline serum beta-2 microglobulin level (≤2.5mg/L versus >2.5mg/L), prior therapy (prior treatment with high-dose chemotherapy and stem-cell transplant or not), and number of prior anti-myeloma regimens (1 versus ≥2).

Superiority of Len/Dex

Studies MM-009 and MM-010 were phase III randomised, double blind, placebo controlled, parallel group trials. Results from a pooled analysis of data from studies MM-009 and MM-010 trials, with a median extended follow-up of 48 months, confirmed significant response outcomes and significant OS benefit with Len/Dex in relapsed or refractory multiple myeloma. These data demonstrated asignificant OS benefit despite nearly half of the patients in the control arm of the study receiving lenalidomide at the time of disease progression or study unblinding.[32]

Superiority of Len/Dex after one prior therapy

Subset analysis from studies MM-009 and MM-010 indicated that TTP, PFS and OS were significantly prolonged and quality of response was superior, when Len/Dex was administered at first relapse compared with its use as a later line of treatment.[5] Subsequent analysis demonstrated that the efficacy of lenalidomide is consistent regardless of prior therapy used[44]; and the analysis

of patient-level data showed benefits in PFS and OS for those patients which had previously received only one previous therapy.[100] Taken together this evidence suggests Len/Dex is a suitable second-line treatment option for multiple myeloma.

Evidence for comparator treatments

The systematic literature review highlights the lack of randomised clinical evidence for retreatment with bortezomib or other comparator treatments used at second line.

The most appropriate evidence for retreatment with bortezomib came from a non-RCT and is therefore not as robust as the RCT evidence for Len/Dex. The median duration of response following bortezomib retreatment was 12.6 months (range 0–37.7 months), with 35% (95% CI 20.6–51.7) of patients still responders at data cut-off. Median TTP following bortezomib retreatment was 10.5 months (range 0.4–≥39.5 months). Median OS from first diagnosis, after prior bortezomib and after bortezomib retreatment was 9.3, 3.5 and 1.7 years, respectively.[45]

The only evidence available for bendamustine was also from a non-RCT. The overall response rate (≥PR) to bendamustine treatment was achieved by 33 patients (30%), including 2 patients (2%) with CR; 22 patients (20%) had stable disease, while 55 patients (50%) did not respond to bendamustine. Notably, 30 patients (27%) refractory to lenalidomide and 33 patients (31%) refractory to thalidomide and bortezomib were found to respond to bendamustine. Overall, following bendamustine treatment, median PFS was 9.3 months and median OS was 12.4 months.[46]

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

Relevance of evidence base

Clinical efficacy data from two large phase III RCTs supports the use of Len/Dex combination for the treatment of patients who had progressive

disease following one prior therapy. The evidence is based on results in 704 patients – representing a significant body of evidence, particularly given the orphan status of lenalidomide in the US and Europe.

The design of the comparator arm and selection of outcome measures for MM-009 and MM-010 were robust and appropriate for the hypothesis under investigation, given the regulatory landscape and availability of approved comparators at the time the studies were initiated. Neither bortezomib nor thalidomide were approved when the MM-009 and MM-010 trials were initiated. Moreover, while thalidomide has marketing authorisation for the first-line treatment of multiple myeloma, it is not licensed for use in previously treated multiple myeloma.

The ITT population for the MM-009 and MM-010 studies included patients across many different stages of disease, which requires the use of subset and patient-level analysis to demonstrate efficacy in the setting relavant to the decision problem. Importantly, these analyses confirm the principle findings and demonstrate the clinical benefits of treatment with Len/Dex with one prior therapy.

Len/Dex has demonstrated superior myeloma control against placebo/Dex in RCTs across all important sub-groups including age, gender, number and type of prior therapies, renal insufficiency, ECOG performance status, suggesting that the data derived from the two trials are both robust and likely to be reproducible outside of the clinical trial setting.

In comparison to bortezomib monotherapy or in combination with high- dose dexamethasone, chemotherapy [including regimens based on melphalan, vincristine, cyclophosphamide and doxorubicin] and bendamustine, the supporting evidence base for lenalidomide should be considered as superior, robust and supportive of a clear improvement in all clinically relevant outcomes over the comparator treatments for this decision scope.

Len/Dex has a manageable tolerability profile. The most common adverse events ascribed to lenalidomide treatment are haematological in nature –

principally neutropenia and thrombocytopenia. Adverse events of this nature are familiar to, and well managed by, haemato-oncologists.

Available information for bortezomib indicates a similar adverse event profile to lenalidomide with thrombocytopenia and neutropenia forming the 2 most common serious adverse events experienced by patients. Additionally guidelines indicate that bortezomib can cause or exacerbate peripheral neuropathy in up to 30% of patients.[8]

Relevance of outcomes of studies MM-009 and MM-010

The outcome measures and their relevance to the therapy area are previously described in section 6.3.5.

The primary endpoint TTP is a broadly accepted surrogate endpoint used in haematology and oncology studies, but data capture and analysis are subject to limitations. Accurate capture of TTP data requires balanced and precise timing of assessment in each arm of the study and analysis does not include patients who died on therapy, prior to progressing.

Time to first decrease in ECOG performance status is a measure of patient quality of life and functioning which may not be captured through response or survival rates.

OS is considered the most reliable cancer endpoint. It is precise and easy-to-measure endpoint, which documented by the date of death; bias is not a factor in its measurement. When studies can be conducted to adequately assess survival, it is usually the preferred endpoint – it is generally evaluated in randomised controlled studies. Demonstration of a statistically significant improvement in OS could represent a clinically meaningful outcome if the toxicity profile is acceptable.

Performing and analysing survival data include long follow-up periods in large trials where subsequent therapy can potentially confound survival. This was the case for the studies MM-009 and MM-010. The high number of patients (170 out of the 351) crossing over from the placebo/Dex arm onto treatment

with Len/Dex, potentially accounts for the extended OS in the placebo/Dex arm.

The efficacy outcomes used in the phase III studies MM-009 and MM-010 provide an international standard for the assessment of multiple myeloma and represent criteria that were specifically designed for use in efficacy studies.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

External validity of study results

The MM-010 clinical study included 41 sites across Europe and therefore, the results achieved in the broad European population included should be reflective of those to be expected in the population of multiple myeloma patients in England and Wales. Even though study MM-009 took place in the USA and Canada, there is no reason to believe that the efficacy from either of these two trials would not be replicated in UK multiple myeloma patients who have progressed following at least one prior therapy. The strict inclusion and exclusion criteria meant that the range of patients were slightly younger and of higher performance status than might be seen in clinical practice. To examine these particular aspects, a number of sub-group analyses were undertaken. These demonstrated that Len/Dex remained superior in efficacy to placebo/Dex regardless of age, performance status and all other variables investigated.

The dose used in the trials is the same as that detailed in the Summary of Product Characteristics.[1] Patients received a starting dose of 25mg of daily oral lenalidomide or placebo on days 1–21 of each 28-day cycle. All patients also received 40mg of daily oral Dex on days 1–4, 9–12, and 17–20. After the

fourth cycle, 40mg of Dex was administered only on days 1–4. Treatment was continued until the occurrence of disease progression or unacceptable toxic effects.

Recommended treatment duration for lenalidomide in the MM-009 and MM-010 trials was until progression, or unacceptable toxic events.[40, 41] Efficacy was demonstrated in MM-009 and MM-010 trial patients including those who experienced treatment interruptions and dosage reductions.

Oral therapy

Lenalidomide is administered orally, in combination with dexamethasone, and for the first eight weeks of therapy requires the patient to have a full blood count, which can be performed locally by the patient's general practitioner or district nurse providing feedback to the treating consultant.

There are a number of advantages associated with the use of oral cancer therapies over those administered parenterally, particularly in patients travelling long distances to hospitals and where transport may be infrequent. This may be especially relevant in rural parts of England and Wales. Many chemotherapeutic regimes in the relapsed or refractory myeloma setting require parenteral administration, for example bortezomib requires sub-cutaneous or intravenous administration on days 1, 4, 8 and 11 of a 21 day cycle – while this can be given in a day case or outpatient setting, it still requires 4 hospital visits per month.

In a study of 103 patients with incurable cancer who were starting chemotherapy, Liu et al. asked about their preference on route of administration.[31] Ninety percent of patients favoured the oral route whenever it was at least as effective as the intravenous route. They considered that taking oral administration was more convenient, reduced the number of visits to hospital, reduced anxiety, allowed working activities, and avoided the complications due to intravenous administration. Patients said that they preferred oral rather than intravenous administration.

Quality of life is also a concern in cancer therapy, particularly in the relapsed / refractory and palliative setting. In this regard, oral lenalidomide may be preferable because it allows daily administration at home, thus reducing hospital visits. Intravenous treatments usually need the insertion of a central vein catheter or, in the case of a continuous infusion, the use of infusion pumps. Associated complications include localised pain, infection, bleeding, deep venous thrombosis and pulmonary embolism.

Further, costs derived from the administration of intravenous chemotherapy may outweigh those of the drugs themselves. In one study of adjuvant and palliative chemotherapy for breast cancer, drugs accounted for 19% to 36% of the total costs of administration.[112] Additional costs may also include those of hospitalisation, travel for patients, salaries of nurses and infusion equipment supplies. For patients attending hospitals a significant distance from their homes, hotel bills can also be an added expense for the treating health board.

In everyday clinical practice, lenalidomide offers a convenient, once-a-day, oral option for patients with relapsed or refractory multiple myeloma, which may permit fewer hospital visits, and offer patients a preferable treatment option.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

A systematic review was conducted in August 2013 to identify clinical studies for multiple myeloma patients treated with Len/Dex following initial treatment with bortezomib. A precise search strategy was used, including terms for Len/Dex and its comparators (listed in Table 36).

Potential comparators were informed from the draft NICE scope. Key opinion leaders were consulted for advice on inclusion of the identified relevant comparators. Additionally, market research data for second-line therapies and British Society of Haematology (BSH) treatment guidelines for multiple myeloma patients were reviewed.[113-115] Within the search strategy, the defined study population is wider than the one specified in the scope, as the objective was to maximise the pool of potential studies and limit the risk of omitting any useful evidence - since the population relevant to the appraisal is very narrow and search terms could not be defined for second-line therapy.

Table 36: Comparators for Len/Dex included in the final scope and in the searches

Comparators
Bortezomib monotherapy and bortezomib in combination with high-dose dexamethasone
Chemotherapy including regimens based on melphalan, vincristine, cyclophosphamide and doxorubicin
Bendamustine

In order to ensure the published literature was comprehensively reviewed, a wide range of databases was searched. These included: Medline, Embase, Cochrane Library, NHS EED, HTA database, DARE, CINAHL and Econlit, along with subject-specific conference proceedings of ASH, ASCO and EHA.

In addition to the formal electronic searches, reference lists of included cost-effectiveness and quality-of-life studies identified were hand searched and scanned for additional publications of relevance to the NICE decision problem.

Having identified studies from a wide range of databases, the titles and abstracts were reviewed in detail to assess their relevance for informing the overall decision problem. Table 37 shows the inclusion criteria for assessing the relevance of the different studies.

Table 37: Inclusion and exclusion criteria and rationale for each criterion

Inclusion criteria		
Category	**Inclusion criteria**	**Rationale**
Study type	Full economic evaluation (including cost-consequence, cost-minimisations, cost effectiveness, cost-utility and cost-benefit evaluations) that compares two or more interventions	The aim of the review was to identify relevant economic evaluations
Population	Adults with multiple myeloma who had previously been treated with bortezomib	This is the relevant patient population
Interventions	The intervention of interest was Len/Dex compared to one of the listed comparators (Table 36)	
Outcomes	Incremental costs and QALYs; any other measure of effectiveness reported together with costs	The aim of the review was to identify relevant economic evaluations, which must report costs
Comparators	The comparators included in the search are listed in Table 36	The comparators for the literature search were selected in accordance with the final scope

Exclusion criteria		
Category	**Exclusion criteria**	**Rationale**
Publication type	Letters; editorials; reviews of economic evaluations (although reference lists of these were be hand-searched)	These are not primary study publications.

Two reviewers independently inspected each reference (title and abstract) identified by the literature search and applied study selection criteria. When abstracts were considered potentially relevant, the full article was obtained and inspected by the same 2 reviewers.

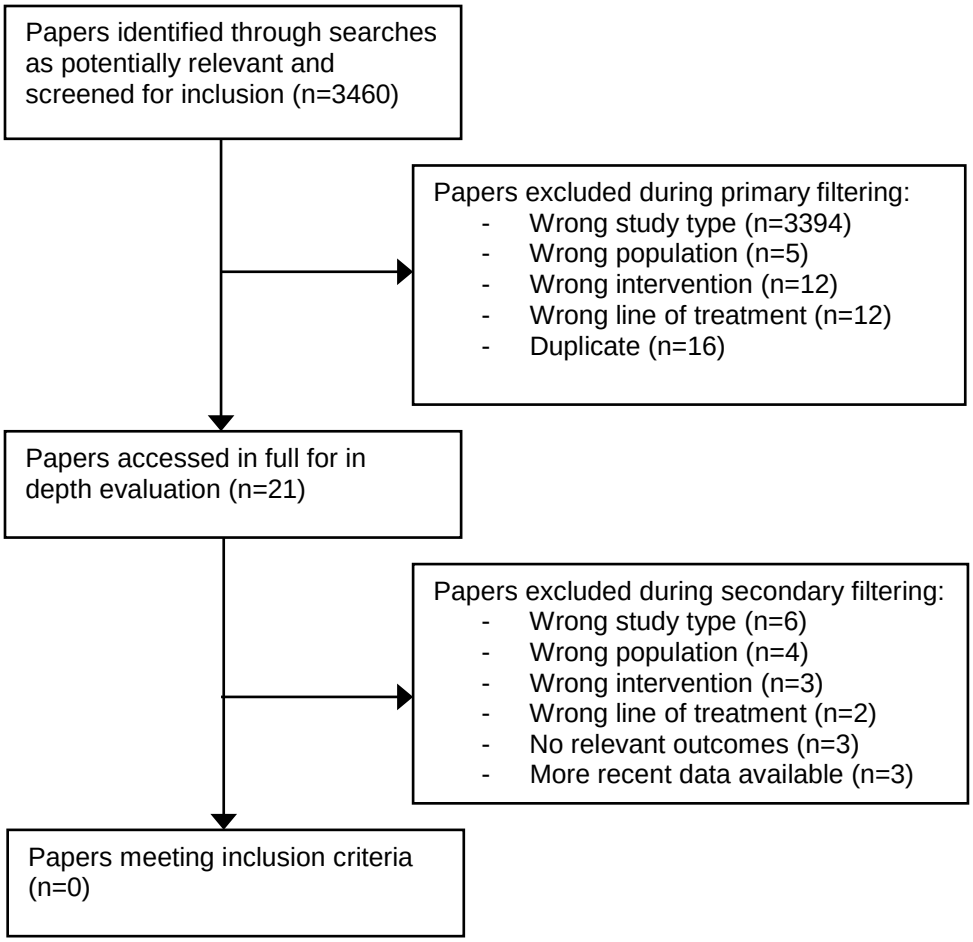
Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

Identification of Relevant Studies

As discussed in section 7.1.1 a range of studies were identified and their relevance assessed according to the inclusion/exclusion criteria described in Table 37. As illustrated by Figure 20, at the primary review the majority of the studies failed to meet the inclusion criteria. At the secondary review, no studies met the inclusion criteria. Therefore, no studies were found that evaluated the cost-effectiveness of bortezomib following an initial treatment with the same drug.

Figure 20: Identification of cost-effectiveness studies of relevance to the decision problem



7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[i] or Philips et al. (2004)[ii]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

No relevant studies were identified that warranted a full review.

[i] Drummond MF, Jefferson TO (1996) 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.

[ii] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

7.2 De novo analysis

Patients

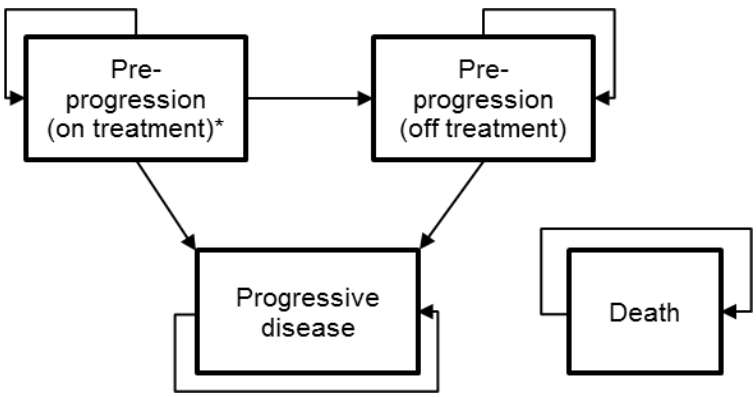
7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

In line with the NICE decision problem the economic evaluation considers adults with multiple myeloma for whom thalidomide is contraindicated and whose disease has progressed after at least 1 prior treatment with bortezomib. This population is more restrictive than the SPC for lenalidomide which covers the treatment of multiple myeloma in adult patients who have received at least one prior therapy. Results from the clinical trials have been adjusted to take into account the population of interest (see section 7.3.2).

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

Figure 21: Model structure



*All patients enter the model in the pre-progression health state.

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

Structure

The model has been developed in a partitioned survival structure. Survival is partitioned into 2 health states: pre-progression and post-progression. Pre-progression patients can be either on or off second-line therapy. Death is a final, absorbing state, to which patients can move from any other health state. This model structure is identical to that used by Picot et al (2011) in their evidence review of NICE technology appraisal 228.[13] The model structure allows costs and outcomes to be captured from the clinical pathway relevant to the NICE decision problem.

Clinical pathway

The clinical pathway followed by patients is shown in Figure 22. Patients enter the model having been treated with bortezomib at first-line, since these patients are unable to tolerate thalidomide. A number of treatment options are routinely used at second-line and these are reflected in the model.

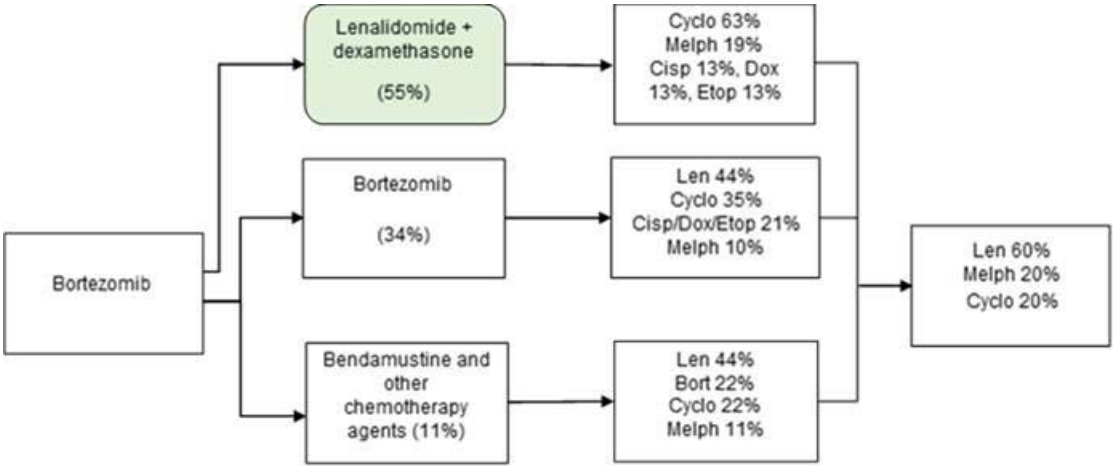
A brief survey was conducted among haematology consultants in England to determine the current use of treatments stated in the NICE final scope. A total of seven consultants were contacted for their view, with five providing a response (see section 7.3.5 and appendix G for further detail). Results from this survey are presented in Table 38.

Table 38: Market share estimates from a survey of clinicians in England

1st Line Treatment	2nd Line rrMM	Proportion use in UK clinical practice	Range (%)
Bortezomib	Bortezomib (either as monotherapy or in combination with high-dose dexamethasone)	34%	15-50
	Lenalidomide (via Cancer Drugs Fund)	55%	35-80
	Bendamustine	6%	1-10
	Chemotherapy including regimens based on melphalan, vincristine, cyclophosphamide and doxorubicin	5%	0-10
rrMM, relapsed or refractory multiple myeloma.			

Results from a larger (n=75 in the UK) previously conducted EU5 market share study on treatments used at first relapse in multiple myeloma (following any initial treatment) indicated that in the UK bortezomib (70%) and lenalidomide (21%) are the most commonly used treatments followed by thalidomide (5%) and bendamustine (4%) which account for very limited use.[116] Other chemotherapy agents were not included in this study. Even though this market research did not specifically consider the treatment pathway being appraised by NICE, the results are helpful in validating the percentages obtained from the smaller sample in Table 38.

Figure 22: Current treatment pathway with the proposed introduction of lenalidomide as a second-line treatment[iii]



Green shading = lenalidomide position under appraisal; Market shares taken from Table 38 for second-line patients and UK registry data for later lines of treatment [117]; Cisp, cisplatin; Cyclo, cyclophosphamide; Dox, doxorubicin; Etop, etoposide; Len, lenalidomide;Melph, melphalan.

Based upon the current treatment pathway >75% of second-line treatment is with bortezomib if lenalidomide use is not considered. The market share of bortezomib is likely to rise following the recent EMA label extension for retreatment in relapsed myeloma. Bortezomib retreatment is therefore considered as the base case comparator within the model presented. Additionally, although multiple sources of evidence exist regarding the efficacy of bortezomib in this setting only one source of information was found for bendamustine following treatment with bortezomib and no sources were found for any of the chemotherapy agents listed in the final scope. However, for the purposes of completeness, comparisons with these treatments are provided as scenario analyses.

It is necessary to capture all relevant costs over the lifetime of these patients, and therefore subsequent lines of treatment are included in the model. Following second and third relapse, 'real-world' treatment pathway data from the Haematological Malignancy Research Network (HMRN) show that multiple myeloma patients are treated with a variety of different therapies. [117]The HMRN is an on-going UK-based registry of newly diagnosed haematological cancer patients, established in 2004, with a view to providing robust and generalisable evidence.

[iii] Note that third-line treatments do not sum to 100% because (a) the use of typical combination therapies, which include dexamethasone and prednisolone, have not been shown on the diagram, but are included in the cost-effectiveness analysis, and (b) some patients receive more than 1 agent.

In the base case analysis, patients receive Len/Dex following discontinuation of bortezomib. For patients who do not receive Len/Dex third line, the varied use of treatments following second or third relapse is incorporated in the model as current management 'baskets' of treatment based on the treatments presented in Figure 22. Incorporating a mix of subsequent treatments within the model matches the approach taken in NICE TA228.[14]

Data used within the model

The model uses data predominantly from trial MM-010 for lenalidomide. Data from MM-010 has been selected for the following reasons:

- This trial has a European patient population and is therefore the most relevant to the decision problem.
- Pooling results from separate studies is not appropriate as this breaks randomisation[118] and as data are only available from single arms of trials no meta-analysis, indirect or mixed treatment comparison is possible.
- The results of MM-009 and MM-010 are comparable (section 6.5):
    - ORR 61% in MM-009 and 60% in MM-010
    - Mean PFS 21 weeks in MM-009 and 20 weeks in MM-010
    - Median PFS 16.6 months at second line in MM-009 and 13.3 months at second line in MM-010
    - Median OS 29.6 months in MM-009, not reached in MM-010
    - Median OS 50.1 months at second line in MM-009 and not reached at second line in MM-010
    - 27.7% died within trial in MM-009 and 26.7% in MM-010

Data for the primary comparator therapy (bortezomib retreatment) are taken from available published literature (Taverna 2012[45]), which was the only source containing both OS and PFS where 100% of the study population had been pretreated with bortezomib. Information from single arm trials has been used and adjusted where possible for differing baseline characteristics (section 7.3.2). An MTC was not possible as all of the comparator information consisted of either observational or phase II studies with no common

treatments to the lenalidomide trials. It was not possible therefore to construct a network of evidence.

7.2.4 Please define what the health states in the model are meant to capture.

The model consists of four unique health states: pre-progression (on-treatment and off-treatment), post-progression and death. Pre-progression captures patients who have not experienced a disease progression on second-line treatment, as defined by within the lenalidomide CSR (Table 7 and section 9.7.1.3.1).[87]

Progression, time on treatment and survival are modelled using parametric PFS, TTF and OS curve fits derived from MM-010 patient-level data.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The main aims of therapy are to prolong survival and maintain a good quality of life by controlling the disease and relieving symptoms (section 2.1).[8] Multiple myeloma is characterised by a sequence of relapses, where treatments eventually cease to have a therapeutic effect and the patient experiences disease progression impacting quality of life.[8]

The model structure captures within its health states the two key aspects of multiple myeloma – survival and quality of life which is impacted by disease progression and the effects of treatment being received.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 39: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	25 years	Lifetime time horizon (98.8% of patients have died)	NICE Guide to the methods of technology appraisals [119]
Cycle length	28 days	This is length of one lenalidomide treatment cycle	Trial CSR[87] Lenalidomide SPC[1]
Half-cycle correction	Yes	Standard practice	
Were health effects measured in QALYs; if not, what was used?	Health effects were measured in QALYs		
Discount of 3.5% for utilities and costs	3.5%	NICE reference case	NICE guide to the methods of technology appraisals
Perspective (NHS/PSS)	The perspective is that of the NHS and PSS	NICE reference case	NICE guide to the methods of technology appraisals
CSR, case study report; NHS, National Health Service; PSS, personal social services; SPC, summary of product characteristics; QALYs, quality-adjusted life years.			

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Lenalidomide and bortezomib are included in the model as per their authorised doses. Dexamethasone is incorporated based upon the mean dose given in the MM-010 trial. These dosing regimens are consistent with the SPC.[120]

Other comparators and subsequent therapies are implemented based upon their SPC documentation or, where a number of dosing regimens are available, based upon the doses used within the clinical trials used to estimate efficacy.

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated

in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators.

No continuation rule other than the rules stated in the SPC has been applied.

7.3 Clinical parameters and variables

7.3.1 Please demonstrate how the clinical data were implemented into the model.

Overview

Patient level data from the MM-010 clinical study were used to inform all model inputs for lenalidomide. Transition probabilities, based on fitted parametric survival curves, were informed by TTF, PFS and OS. The sections below provide a full description of how the clinical parameters are included in the model. Adverse events and toxicity are included in the model based upon the rates of treatment-emergent adverse events included within NICE technology appraisal TA171 at severity grade 3 and 4.[3]

Transitions between health states

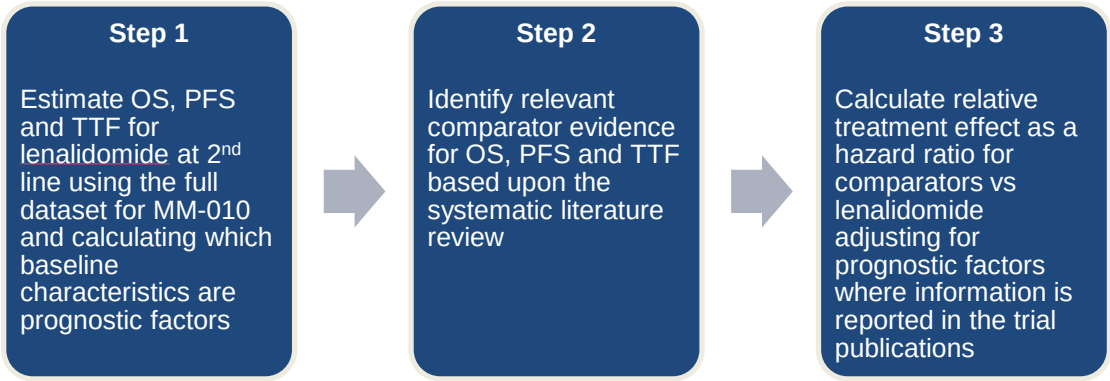
Multivariable equations were developed to model OS, PFS and TTF for lenalidomide, considering a range of fitted multivariate parametric curve forms using MM-010 patient-level data. The use of multivariable equations allows standard parametric curve fits to be adjusted to take into account differences in baseline population characteristics (for example line of treatment and disease severity). The use of these multivariable equations was particularly important within this submission for two reasons:

- To allow adjustment for differing baseline characteristics between the trials for lenalidomide and those available for comparators as no direct or indirect comparative information was available for analysis
- To allow the use of all relevant information from the available trials due to the small sample sizes available for a second-line population: available comparator information did not provide

subgroup analysis by line of treatment and sample sizes were limited within the MM-009 and MM-010 trials

Figure 23 shows the process used to model OS, PFS and TTF for lenalidomide versus comparator treatments.

Figure 23: Modelling process for OS, PFS and TTF



OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Survival analysis methods

The full MM-010 dataset was used to inform which variables should be included in the survival models for the relevant, second-line population. As such, the models presented have been developed such that the baseline hazard reflects estimates for lenalidomide patients treated in a second-line setting. Using the full dataset increased the sample size and preserved the benefits associated with trial randomisation in informing this analysis.

Analysis conducted by Dimopoulos et al, showed that for patients with 1 prior therapy, hazard ratios (HRs) for Len/Dex were similar across all subgroups regardless of type of prior therapy. Although, it is noted that data at second line did not include prior bortezomib due to low patient numbers.[44] Data from Mateos et al shows similar response rates for patients receiving prior bortezomib to those receiving prior chemotherapy.[43] Therefore efficacy from all second-line patients was used to model efficacy for patients receiving prior

bortezomib within the model.

Six parametric distributions (exponential, Weibull, log-logistic, log-normal, Gompertz and gamma) were explored for each clinical outcome (OS, PFS, TTF). The fit of the each parametric model to the observed data were explored using:

- Log cumulative hazard plots
- Observed smoothed hazard plots versus parametric equivalents
- Observed Kaplan–Meier survival plots versus parametric equivalents
- Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics

The multivariable parametric models were developed to include a series of baseline risk factors considered to be predictors of the outcome. Baseline risk factors considered to be potentially prognostic of clinical outcomes were derived from the MM-010 clinical study report and were:

- Age (years)
- Sex
- Disease stage (I, II or III)
- Number of prior anti-myeloma regimens
- Time since diagnosis of multiple myeloma
- ECOG performance score (0,1,2+)
- Beta-2 microglobulin count (mg/L)
- Number of prior stem cell transplants
- Presence or absence of bone lesions

Variables were initially reviewed for missing data. A separate category (unknown) was created for categorical variables with missing estimates. Binary and categorical variables were reviewed to confirm whether the existing categorisations were satisfactory and to ensure there were sufficient numbers of patients in each group to permit analysis. Continuous variables were reviewed to confirm whether they showed evidence of a linear relationship with the clinical outcome of interest. An initial set of variables

were identified for each endpoint using backwards stepwise elimination (using $p<0.05$), cross validated using forwards stepwise selection (using $p<0.1$). Selected variables were analysed for evidence of collinearity using a review of variance inflation factor (VIF) statistics. If collinearity was evident (VIF>10), only the variable that showed the strongest relationship with the outcome and greatest face validity was retained. Cox-Snell residuals were examined to assess the final model goodness of fit.

The effect of each independent categorical variable was assessed using proportional hazard (PH) and accelerated failure time (AFT) assumptions. Alternative approaches were considered if a standard parametric approach provided a poor fit to observed data, or given evidence of PH or AFT violation for the variables included in the multivariable regression model.

These approaches were based on methods recommended in the NICE Decision Support Unit Technical documentation[121] and included exponential piecewise modelling and a time dependent Weibull model. The exponential piecewise approach splits survival time into series of time intervals and provides separate estimates of the hazard rate (and potentially hazard ratio) for each time interval. A time dependent Weibull approach includes a time-varying dependent variable.

Beta-2 microglobulin count, time since diagnosis of multiple myeloma, number of prior therapies, baseline presence or absence of bone lesions, and ECOG performance score were all found to be significant predictors of PFS, TTF and OS in MM-010 (consistent with analysis conducted for TA171). For all models, the duration of multiple myeloma and number of prior therapies are not used because multiple myeloma duration was centred on the mean duration (4.5 years in MM-010). Therefore the baseline hazard predicts survival for this duration. Additionally, the population of interest is treated in the second-line setting. As such these two terms were not required to model the population of relevance.

Survival analysis results

Progression-free survival

The Kaplan–Meier PFS curve for Len/Dex is shown in Figure 24. The hazard for lenalidomide appeared to decrease over the initial study period (until approximately 24 months), after this time point the hazard increased, although later estimates were based on fewer observations (see log-log plot; Figure 25).

A review of the AIC and BIC statistics indicated that the log-logistic distribution followed by the lognormal distribution provided the best statistical fit to the observed data (Table 40).

Figure 24: Kaplan–Meier plot and fitted log-logistic model for PFS

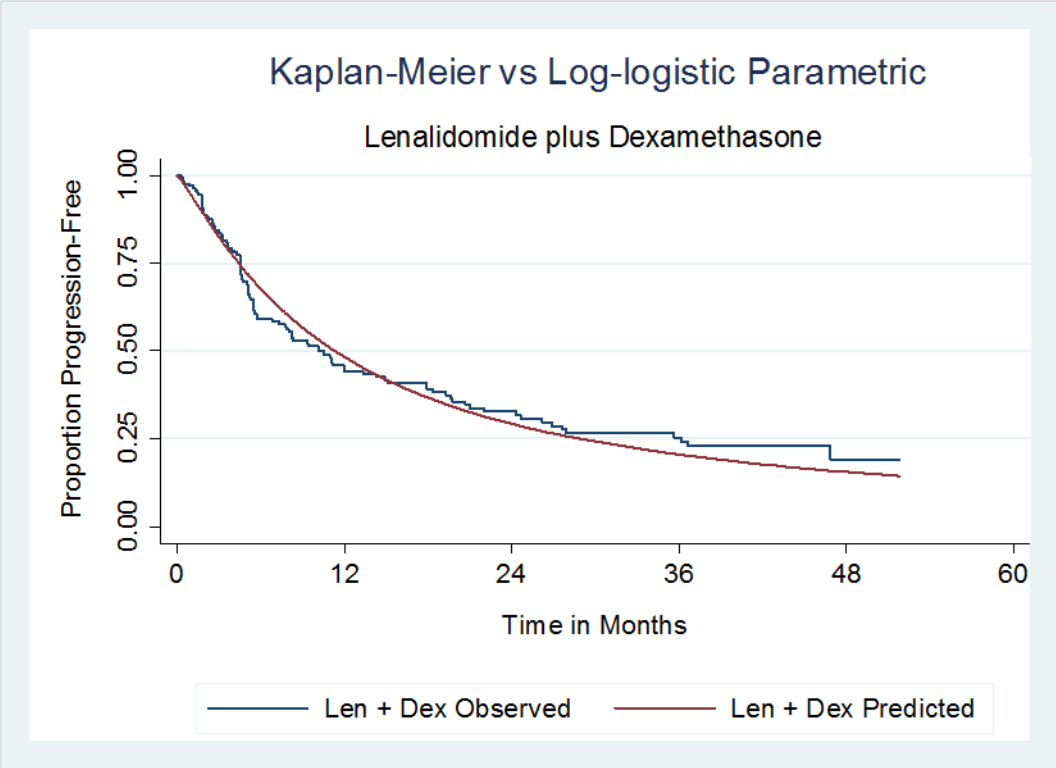
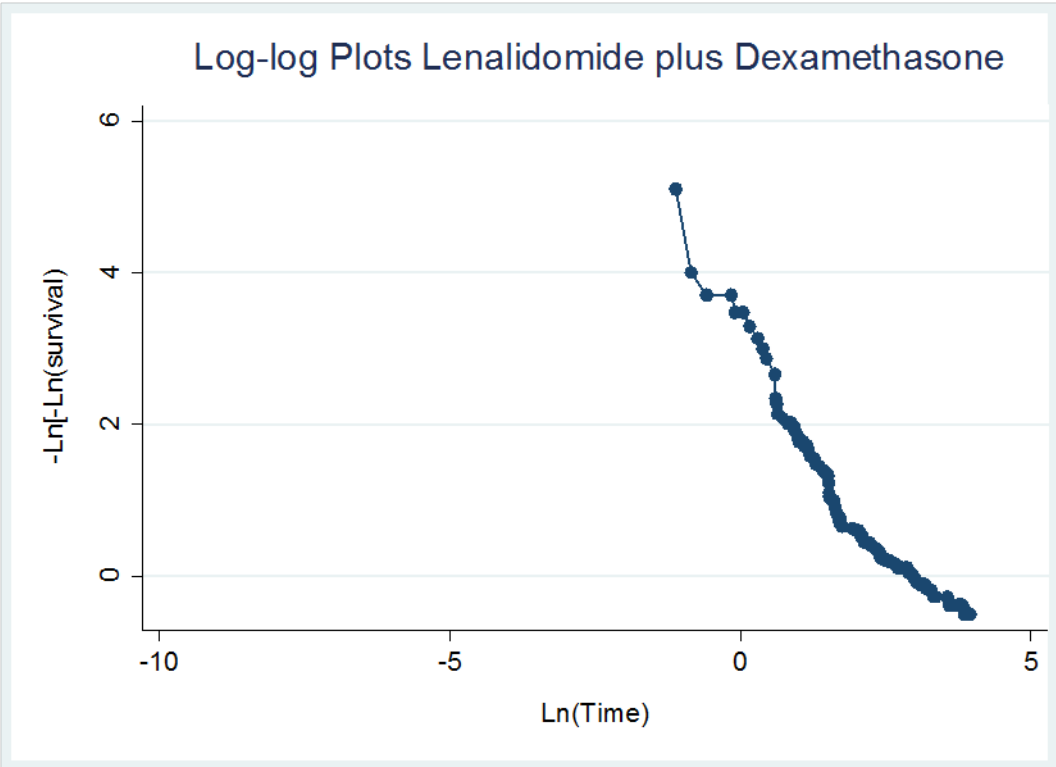


Figure 25: Log-log plot for PFS



Negative values appear on the x-axis because the time variable was in month units, and a duration of less than 1 month will produce a negative number on the log-scale.

Table 40: AIC and BIC statistics for PFS models (MM-010)

Model	AIC	BIC
Exponential	985.31	993.03
Weibull	980.90	996.34
Gompertz	944.59	960.03
Log-normal	930.56	946.00
Log-logistic	**924.49**	**939.93**
Gamma	931.07	954.24

A visual review of Kaplan–Meier plots against the predicted survival curves suggested that lognormal, log-logistic and Gompertz distributions provide the best fit of the data (see appendix H). However, the Gompertz distribution appeared to predict a particularly low hazard in the later phase of the trial (not consistent with observed data), resulting in particularly extensive post-trial survival time. Use of Weibull or exponential curves would not be appropriate due to a lack of monotonic hazards.

In view of all available evidence, the log-logistic distribution was considered the optimal distribution for the base case analysis (Figure 24). The lognormal is included as a sensitivity analyses. Beta-2 microglobulin count was the only significant, non-redundant predictor of progression-free survival. The resulting regression models are presented in Table 41.

Table 41: PFS regression model estimates

Parameter	Coefficient estimate	
	Log-logistic model	Lognormal model
Intercept term	-0.779	-0.813
Beta-2 microglobulin >2mg/L	3.116	3.151
Ln(gamma)	-0.218	0.308

Time to treatment failure

The Kaplan–Meier curve for Len/Dex TTF is shown in Figure 26, based upon MM-010 data. The hazard for lenalidomide again appeared to decrease over the initial study period (see log-log plot; Figure 27). TTF demonstrated similar trends to PFS data since patients discontinued lenalidomide therapy upon progression according to study protocol.

The AIC and BIC statistics indicated that the log-logistic distribution followed by the Gompertz, gamma and Weibull distributions provided the best statistical fit of the observed data (Table 42). Kaplan–Meier plots versus the predicted survival curves for each distribution also indicated that these four distributions provided the best fit of the data. However, similar to PFS, the Gompertz distribution appeared to predict a particularly low hazard in the later phase of the trial (which was not consistent with observed data) and resulted in particularly optimistic post-trial survival time (i.e. time before treatment failure). Use of Weibull or exponential curves would again not be appropriate due to a lack of monotonic hazards. Curve fits for all of the OS models tested are provided in appendix H.

Figure 26: Kaplan–Meier plot and fitted log-logistic model for TTF

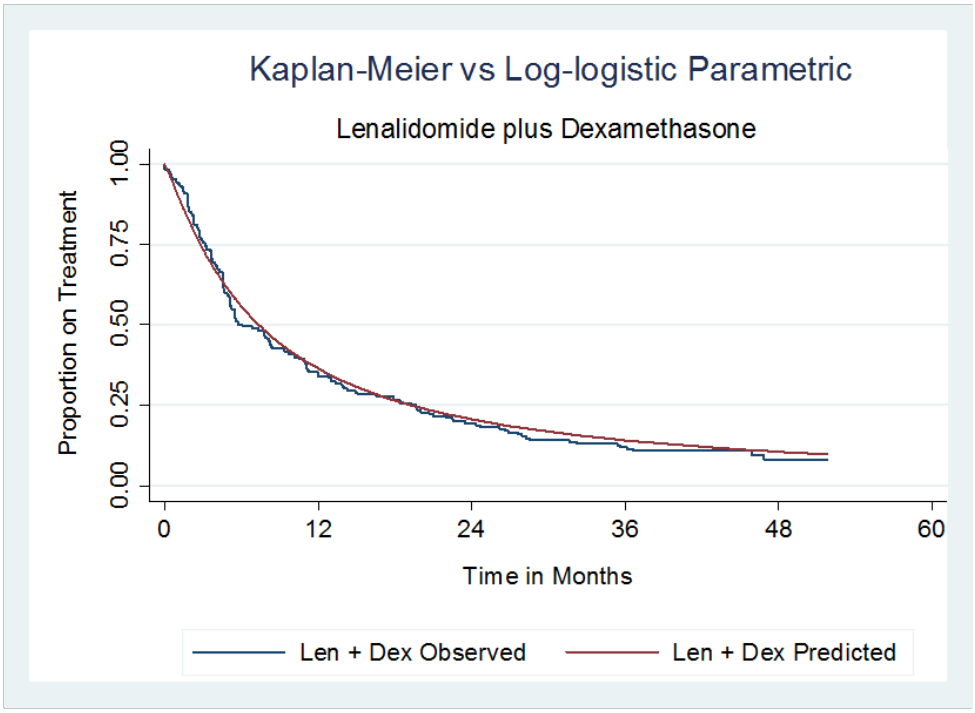


Figure 27: Log-log plot for TTF

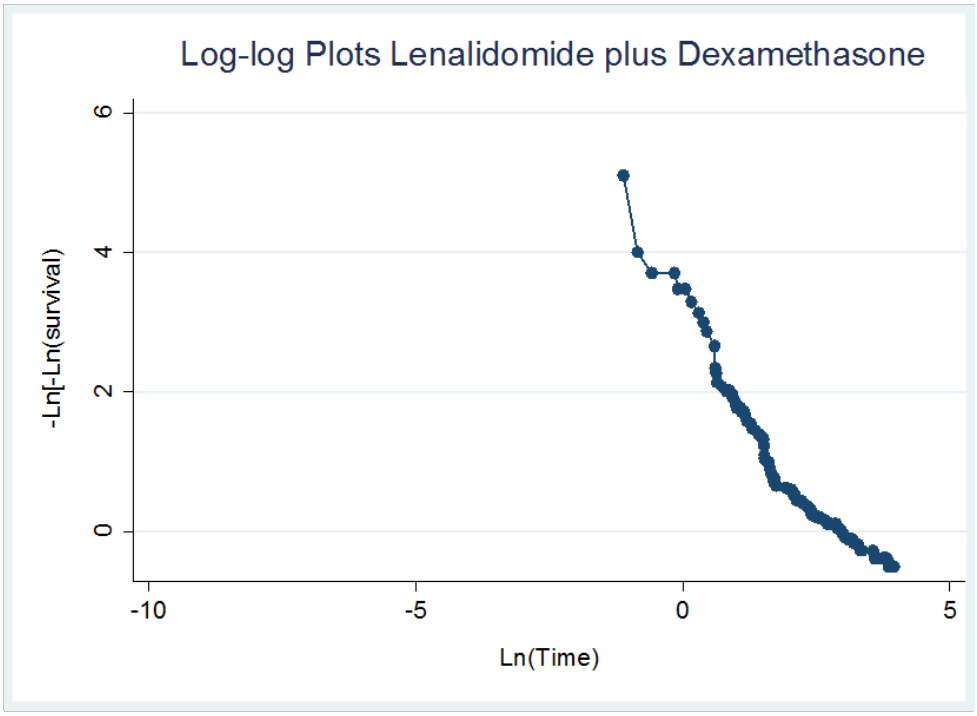


Table 42: AIC and BIC statistics for TTFmodels (MM-010)

Model	AIC	BIC
Exponential	1212.52	1220.24
Weibull	1196.99	1212.43
Gompertz	1174.56	1190.01
Log-normal	1237.53	1252.97
Log-logistic	**1158.20**	**1173.64**
Gamma	1174.20	1197.37

After consideration of all evidence, a log-logistic parametric model (Figure 26) was considered to be the most appropriate survival modelling approach for TTF, with a lognormal model considered for sensitivity analyses. The use of a lognormal model ensures the same distribution can be applied for both PFS and TTF, which is seen to be necessary given the similarity of the two measures, however, it should be noted that the lognormal distribution does not provide as good a fit to TTF as PFS and therefore results using this distribution should be reviewed with caution. Beta-2 microglobulin count was the only significant, non-redundant predictor of TTF (as was seen with PFS). The resulting regression models are presented in Table 43.

Table 43: TTF regression model estimates

Parameter	Coefficient Estimate	
	Log-logistic model	Lognormal model
Intercept term	2.678	2.663
Beta-2 microglobulin >2mg/L	-0.731	-0.858
Ln(gamma) / Ln(sigma)	-0.153	0.669

Overall survival

The Kaplan–Meier curve for OS among Len/Dex MM-003 subjects is shown in Figure 28. There is evidence of increasing hazard for lenalidomide patients during the study period, a trend which appears greatest at the end of the study, although estimates at the end of the study period would have been based on fewer observations due to censoring (Figure 29).

Figure 28: Kaplan–Meier plot for OS

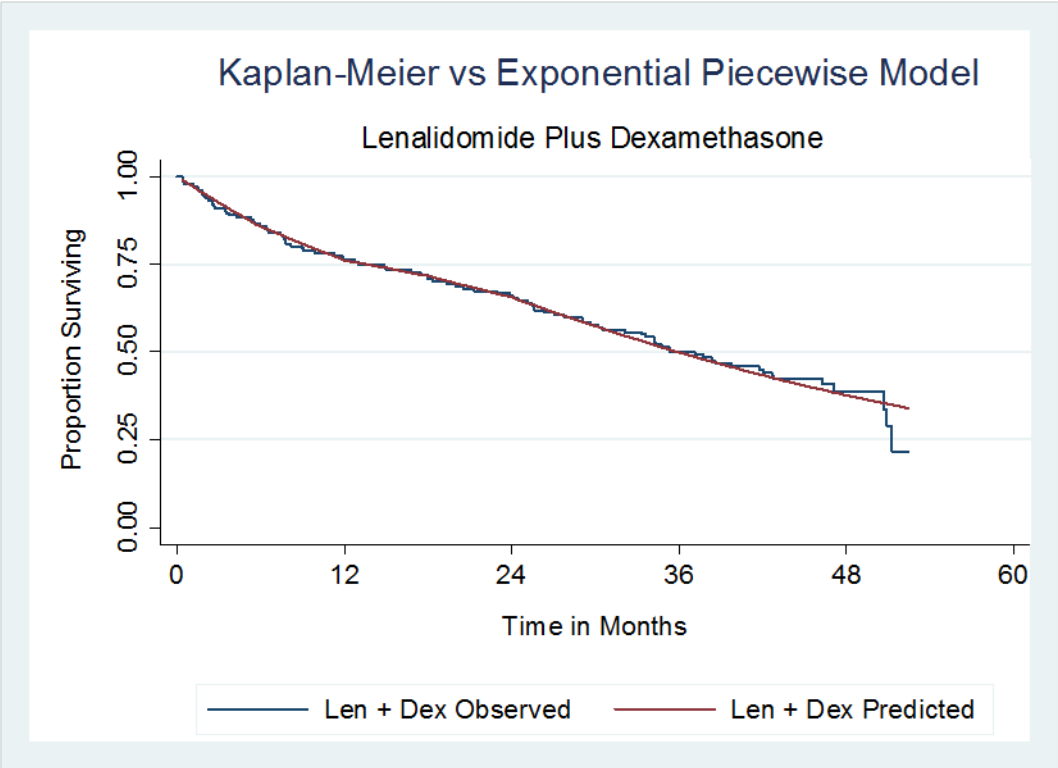
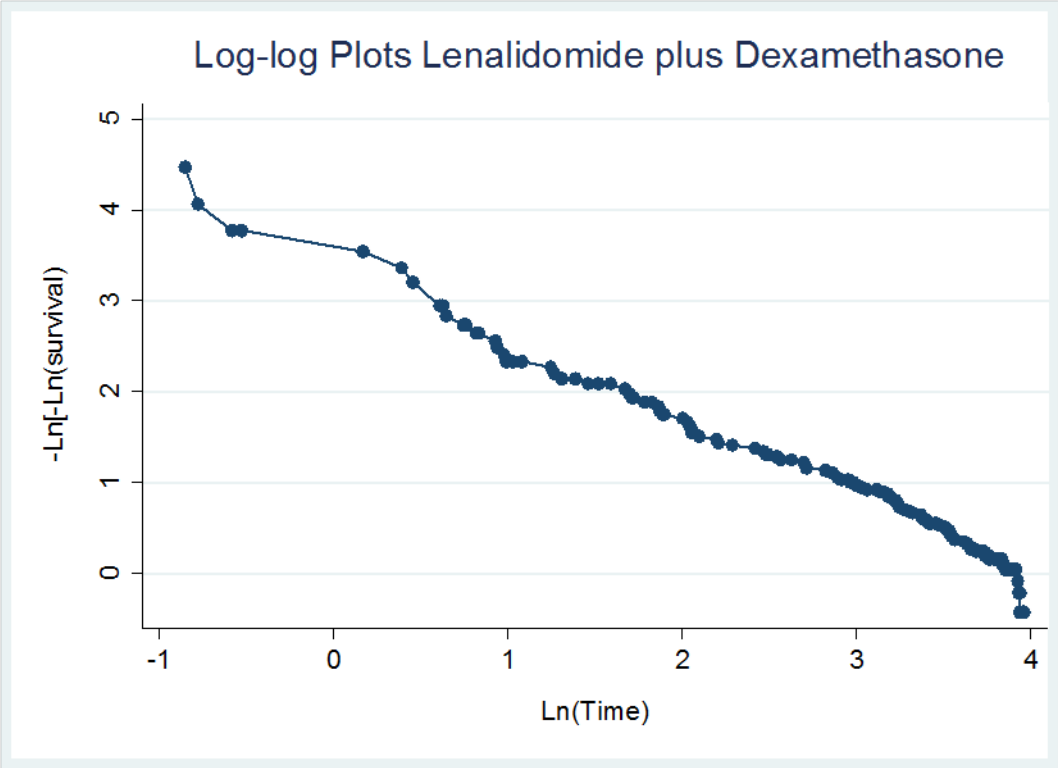


Figure 29: Log-log plot for OS



The AIC statistic indicated that the Weibull distribution provided the best statistical fit of the observed data, while the BIC statistic indicated that the exponential distribution provided the best fit. Fit statistics were similar between all distributions, however, and the Gompertz and gamma functions also appeared to offer a comparable fit.

Table 44: AIC and BIC statistics for OS models (MM-010)

Model	AIC	BIC
Exponential	979.62	**987.34**
Weibull	**978.12**	993.57
Gompertz	980.50	995.95
Log-normal	989.30	1004.75
Log-logistic	984.05	999.49
Gamma	981.19	1004.35

The following non-redundant variables were found to be strong predictors of mortality in MM-010:

- Beta-2 microglobulin count (<2.5 or ≥2.5mg/L)
- ECOG performance score (0, 1, 2+)
- The presence or absence of bone lesions

There was, however, evidence of PH (and AFT) violation for the beta-2 microglobulin count variable. An alternative parametric survival modelling approach was therefore considered in order to improve the model fit and account for the observed PH violation. This employed a piecewise exponential model, with survival time split into 6 month intervals. This exponential piecewise model appeared to best capture observed trends and provide a plausible extrapolation of survival. As such, in view of all available evidence, this was considered the optimal distribution for the base case analysis (Figure 28). The Weibull model was included for sensitivity analyses, however, this model required adjustment as in the long-term survival was predicted above that of the general population therefore results presented using the Weibull model should be viewed with caution. The regression coefficients for these models are presented in Table 45. Curve fits for all of the OS models tested are provided in appendix H.

Table 45: OS regression model estimates

Parameter	Coefficient estimate	
	Piecewise exponential model	Weibull model
Intercept term	-4.673	-4.451
Beta-2 microglobulin >2mg/L	0.613	0.611
ECOG score: 1	0.101	0.101
ECOG score: 2	0.621	0.625
ECOG score: unknown	-0.046	-0.020
Bone lesions present	0.440	0.432
Time: months 6≤ t <12	-0.327	N/A
Time: months 12≤ t <18	-1.316	N/A
Time: months 18≤ t <24	-1.003	N/A
Time: months 24≤ t <30	-0.730	N/A
Time: months 30≤ t	-0.449	N/A
Ln(gamma, intercept)	N/A	-0.240

Comparative efficacy

There is a lack of good quality published evidence for second-line patients who have been previously treated with bortezomib. To obtain plausible estimates of clinical outcomes for comparator therapies included in the analysis, a systematic literature search was undertaken for comparator clinical data, see section 6.1. Sources obtained and used for analysis of comparative efficacy are presented in Table 46.

Median OS and PFS outcomes were derived from the sources (as means were not reported) and were used to calculate HRs for each comparator relative to Len/Dex in MM-010. A crude approximation of a hazard ratio for lenalidomide and each comparator (bortezomib, bendamustine, cyclophosphamide and melphalan) was obtained by comparing median survival estimates (PFS and OS) between studies of interest. This analysis assumes that progression/mortality occurs at a constant rate in both studies and that studies are exchangeable (i.e. have been conducted with comparable populations and trial conditions). In order to improve exchangeability, the multivariable parametric models designed to predict PFS and OS (detailed in the sections above) were used to adjust median survival estimates for lenalidomide. Baseline characteristics that were predictive of progression or mortality and had been reported in the study of interest were

entered into the lenalidomide risk equations and adjusted median survival estimates were derived.

Two hazard ratios for each treatment versus lenalidomide were estimated. The first hazard ratio estimate compared median survival estimates from each comparator to the observed median survival for lenalidomide patients in MM-010 (n=176), that is without adjustment for differing baseline characteristics. The second hazard ratio estimate compared median survival estimates for each comparator to adjusted median survival estimates from MM-010 – this analysis was used within the model where the papers presented enough detail to allow adjustment.

It was assumed that the HR for TTF would be the same as for PFS as the curve fits for lenalidomide because these two variables are similar and no information on TTF was presented in any of the evidence identified.

Bortezomib retreatment HRs obtained from Taverna et al were applied in the base case analysis.[45] This source provided HRs for both PFS and OS and consisted solely of patients being retreated with bortezomib. Additionally, it was possible to adjust the hazard ratio for OS to taking into account differences between study populations in duration of multiple myeloma.

Just 19% of subjects in the White et al study were classified as being retreated with bortezomib[42], which is the only alternative source for comparative OS. The recent study by Petrucci et al for bortezomib retreatment only reported TTP for responders to retreatment and, as such, would provide a much more conservative, best-case estimate of comparative PFS for bortezomib.[53] Additionally the patient group in this study consisted of previous responders only.

Other comparators are included as scenario analyses. For the comparative efficacy of bendamustine, HRs obtained from the Damaj et al paper were retrieved and applied [46], no other alternative estimates were identified from the literature. In the absence of information for other chemotherapy agents, the HRs available for bendamustine were applied in the model.

The HRs included in the model are presented in Table 47. For all comparators the HR for PFS is applied to TTF, as the curves fitted to these variables are similar in nature within the lenalidomide dataset. Full details of the methods used to estimate these HRs are provided in appendix I.

Table 46: Details of studies analysed for comparative efficacy

	Petrucci 2013[+53]	Hrusovsky 2010[50]	Taverna 2012[+45]	Dispenzieri 2010[80]	Min 2007[122]	White 2013[42]	Damaj 2012[46]	Lenalidomide MM-010[87]
Treatment	Bortezomib retreatment						Bendamustine	Lenalidomide
n	50*	60	42	7	57	53	110	176
Country	Europe - 55 centres	Germany & Switzerland	Switzerland	US	South Korea	US & Canada	France	Australia, Europe, and Israel - 55 centres
Median Age	67	65.7	63	63	54.5	65	63	62
Male	57%	55%	52%	50%	41%	57%	61%	59%
Prior Bortezomib (note: at any treatment line)	100%	100%	100%	100%	100%	19%	100%	5%
Median time since diagnosis (years)	4.5	4.3	2.8	n/r	n/r	3.3	n/r	4.2
Number of prior anti-myeloma therapies								
1	12%	n/r	n/r	n/r	n/r	49%	n/r	32%
2+	88%	n/r	n/r	n/r	n/r	51%	n/r	68%
Median number of prior anti-myeloma therapies	n/r	3.7 (range 1-14)	2 (1–11)	n/r	2(range1-3)	n/r	4 (range 1-9)	2 (range 1-3)
Presence bone lesions	n/r	n/r	n/r	n/r	63%	55%	n/r	77%
ECOG Performance Status								
0	n/r	n/r	n/r	n/r	n/r	49%	n/r	44%
1	n/r	n/r	n/r	n/r	n/r	51%	n/r	41%
2+	n/r	n/r	n/r	0%	n/r	-	n/r	13%
Unknown	n/r	n/r	n/r	n/r	n/r	-	n/r	2%
Median number of prior anti-myeloma therapies	n/r	3.7 (range 1-14)	2 (1–11)	1	2 (range 1-3)	n/r	4 (range 1-9)	2 (range 1-3)
% receiving concommitant Dex	72%	63%	64%	n/r	0%	n/r	n/r	100%
% receiving concommitant immunomodulating therapy	n/r	23%	14%	n/r	n/r	n/r	n/r	0%

*only responders were reported [+]TTP used as a proxy for PFS.
Dex, dexamethasone; ECOG, Eastern Cooperative Oncology Group; n/r = not reported in study; PFS, progression-free survival; TTP, time to progression.

Table 47: Comparative efficacy estimates included in the model

Treatment	Variable	Evidence source	Hazard ratio
Bortezomib retreatment	OS	Taverna 2012[45]	1.70
		White 2013[42]	1.42
	PFS	Taverna 2012	1.15
		White 2013	1.76
		Hrusovsky 2010[50]	1.09
		Dispenzieri 2010[80]	1.28
		Petrucci 2013[53]	1.26
		Min 2007[122]	0.84
Bendamustine (and chemotherapy agents)	OS	Damaj 2012[46]	3.00
	PFS	Damaj 2012	1.09

Adverse events

The same grade 3 and 4 treatment-emergent adverse events that were included in the NICE technology appraisal for lenalidomide for multiple myeloma following at least one prior therapy have been included in the present analysis.[3] The adverse events included are, therefore, as follows:

- Anaemia
- Constipation
- Diarrhoea
- Deep vein thrombosis
- Hypercalcaemia
- Neutropenia
- Peripheral neuropathy
- Pneumonia
- Thrombocytopenia

These events have been included by calculating event rates. In order to provide the maximum available safety data the total number of events in MM-010 were divided by the total number of patient years on treatment, obtained from the patient-level study data. This gave the annual adverse event rates which were converted to 28-day cycle rates, as shown in Table 48. These rates are applied on a per-cycle basis for patients on treatment.

For bortezomib, the number of event occurrences reported as part of NICE technology appraisal 228[13], from the VISTA clinical study, were used due to a lack of detailed evidence for this setting from the bortezomib studies identified in the systematic review. The number of each event listed in Table 48 experienced by patients in receipt of bortezomib in combination with melphalan and prednisone or prednisolone (MP) were obtained. These and

the reported median treatment duration (46 weeks) were used to calculate per cycle event rates in the same way as described above. The number of occurrences of hypercalcaemia in bortezomib + MP patients was not reported, and therefore it was assumed to be 0%. The available literature on bortezomib retreatment was reviewed to validate the adverse event rates included in the model (see appendix J).

The adverse events reported in Picot et al[13] for VISTA subjects who received MP for median of 39 weeks were applied in the model for all other comparator therapies. This was applied in the absence of evidence elsewhere.

Table 48: Adverse event rates applied in the economic analysis

Adverse event	Grade	Annual rate (cycle rate)		
		Len/Dex	Bortezomib	Other comparators
Anaemia	3	8.3% (0.6%)	17.7% (1.3%)	26.2% (2.0%)
	4	0.5% (<0.1%)	3.0% (0.2%)	10.3% (0.8%)
Constipation	3	1.4% (0.1%)	0.7% (0.1%)	0.0% (0.0%)
	4	0.0% (0.0%)	0.0% (0.0%)	0.0% (0.0%)
Diarrhoea	3	2.3% (0.2%)	7.7% (0.6%)	0.8% (0.1%)
	4	0.0% (0.0%)	0.7% (0.1%)	0.0% (0.0%)
Deep vein thrombosis	3	3.2% (0.5%)	1.0% (0.1%)	0.8% (0.1%)
	4	0.5% (<0.1%)	0.0% (0.0%)	0.0% (0.0%)
Hypercalcaemia	3	0.5% (<0.1%)	0.0% (0.0%)	0.0% (0.0%)
	4	0.0% (0.0%)	0.0% (0.0%)	0.0% (0.0%)
Neutropenia	3	59.3% (4.4%)	34.0% (2.6%)	31.4% (2.4%)
	4	5.1% (0.4%)	11.3% (0.9%)	19.5% (1.5%)
Peripheral neuropathy	3	1.4% (0.1%)	14.3% (1.1%)	0.0% (0.0%)
	4	0.0% (0.0%)	0.3% (<0.1%)	0.0% (0.0%)
Pneumonia	3	4.6% (0.4%)	5.3% (0.4%)	5.2% (0.4%)
	4	0.5% (<0.1%)	2.0% (0.2%)	1.6% (0.1%)
Thrombocytopenia	3	11.0% (0.8%)	22.7% (1.7%)	21.8% (1.7%)
	4	1.4% (0.1%)	19.4% (1.5%)	18.7% (1.4%)

In the base case analysis, patients on the comparator arm go on to receive Len/Dex following treatment discontinuation and this is in line with current UK clinical practice.[3] These patients become subject to the adverse event rates associated with Len/Dex above. No adverse events are modelled after treatment discontinuation for other subsequent therapies, this is a simplifying assumption applied due to the paucity of evidence and lack of impact of adverse events on the modeled ICER.

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

The time-dependency of transition probabilities is included through the use of parametric survival models. These characterise OS, PFS and TTF over a continuous time scale.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Intermediate outcomes were not used to provide a direct link to final outcomes.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide details[4]:

Celgene consulted with a 2 key opinion leaders and a patient group organisation when it responded to the comparator list in the draft scope. Following the issuance of the final scope for this appraisal, Celgene conducted a brief survey among practicing haematologists to ascertain the comparators specific to the decision problem (appendix G). Due to the limited time frame, no set criteria were established before approaching the experts. An executive medical liaison (an employee of Celgene whose professional role is to engage on scientific matters/clinical trials) with established relationships was tasked to reach out to the experts via email communication. A total of 7 were contacted, of whom 5 responded to the survey. No declaration of potential conflict of interest was sought due to time constraints

[4] 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.

and the fact only 1 question was being asked, in relation to their own current experience / practice.

Clinicians were informed that the question was being asked in relation to this submission and were specifically asked to respond to the question: *"If newly diagnosed multiple myeloma (NDMM) patients receive bortezomib as front line treatment, and have the following treatments as options at second-line, in UK clinical practice what would the percentage use of these treatments be (all adding up to 100%)?"*

The responses were directly sent to the executive medical liaison who then forwarded them to be included in this submission (Table 38). Where the responses did not add up to 100%, an adjustment was made to reflect the appropriate distribution (appendix G).

Responses indicated relatively scarce use of bendamustine and other chemotherapy agents, for which there is a lack of evidence (as shown in section 6). Given the low usage of these treatments reported by clinical expects, they are not considered in the base case cost effectiveness analysis.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

A summary table is provided in appendix N.

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

Outcomes are extrapolated beyond the trial duration through the use of parametric survival models, as described in sections 7.3.1-2 and appendix H. No explicit long-term efficacy assumptions have been made, as any long-lasting treatment effect will occur due to the characterisation of PFS and OS through their parametric models.

In the base case analysis, patients on the comparator model arm receive Len/Dex following the discontinuation of the comparator therapy. These patients are subject to the OS and TTF hazards associated with Len/Dex at second line, as discussed in section 7.3.2. This assumes that the second-line efficacy of Len/Dex is replicated at the third line of treatment, which is a conservative assumption for lenalidomide as this means comparator patients will experience extended survival due to receiving subsequent Len/Dex, even though it is shown to be more effective at earlier lines.[5]

A model scenario analysis is presented whereby Len/Dex is not automatically given following discontinuation of the comparator therapy. In this scenario the cost of treatments beyond the trial duration are based upon real-world third-line and fourth-line treatment of myeloma patients from 2007-2009.[117] These last for 17.2 weeks, and this mean duration takes into account mortality. Patients receive a ‘basket’ of therapies reflecting the mix of therapies likely to be used at third line following initial treatment with bortezomib.

In both the base case model and model scenario described above, the same real-world data are used to determine the cost of further treatment at fourth line. The mean fourth-line treatment duration, which accounts for mortality, is 16.8 weeks.

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Table 49: Model assumptions

Type	Assumption Made	Justification
Prior treatments	The prior use of thalidomide, bortezomib or any other treatment has no impact on clinical outcomes of second-line treatment of multiple myeloma.	This was assumed to utilise the maximum data from MM-010, and is supported by Dimopoulos et al and Mateos et al[43, 44]
Comparator efficacy	The OS, PFS and TTF hazards associated with Len/Dex and comparator therapies are proportional to each other over time, i.e. there is a constant relative hazard, allowing for hazard ratios to be used in estimating relative efficacy.	Necessary assumption to apply hazard ratios to estimates comparator efficacy, in the absence of evidence.
Adverse events at 2nd line	In the absence of other data, the adverse event profile of bortezomib is obtained from TA228 (bortezomib, melphalan and prednisolone). The adverse-event profile of other comparator treatments are assumed to be equal to each other, obtained from the MP arm of TA228.	Applied in the absence of other evidence. TA228 provides the fullest source of adverse event information.
Adverse events beyond 2nd line	No adverse events are modelled during subsequent lines of treatment, following the discontinuation of Len/Dex or the chosen comparator. However, that Len/Dex adverse events are applied when patients move onto this as a third-line treatment.	This is a conservative assumption, made in the absence of evidence for this patient group.
Subsequent treatment	Patients receive subsequent third- and fourth-line treatment (other than Len/Dex at third line) for fixed durations (17.2 weeks and 16.8 weeks). These mean durations were obtained from real-world UK data[117] and account for patients who die. Following fourth-line therapy it is assumed that no further active treatment is given.	Based upon real-world data and likely to reflect clinical practice, where conventional therapies become exhausted over time.
Subsequent treatment	Fourth-line treatment is applied as a 'basket' of therapies, weighted by the proportion of use of each. This is also the case for third-line treatment in the model scenario where Len/Dex is not used at third line.	A simplifying assumption that reflects the wide variety of treatments given in the later stages of multiple myeloma.
Administration appointments	For oral therapies, an appointment is required for the first administration only. This does not apply for combination treatments where one of the therapies is delivered intravenously or subcutaneously however; the cost of an IV administration appointment is assumed to include oral administration. Administration costs are not applied for the first administration of subsequent therapies.	Likely to reflect clinical practice
Transport for treatment administration	Half of all patients require transport to hospital for administration appointments. If more than one appointment is required in a week, it is assumed that patients remain in hospital and only one transportation cost is required.	Assumption based upon treatment for anaemia[123]
OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.		

7.4 Measurement and valuation of health effects

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Multiple myeloma is chronic, debilitating haematological cancer. It has been found to harm overall patient quality of life, and in particular role and social functioning.[124] The condition is characterised by clinical features such as anaemia and peripheral neuropathy[8], while the high intensity of treatments may expose patients to levels of toxicity which further heighten the risk of adverse events.

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Multiple myeloma is characterised by a sequence of relapses, where treatments eventually cease to have a therapeutic effect and the patient experiences disease progression. [8]

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case.

HRQL data were not collected in the MM-010 clinical trials.

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

The lenalidomide clinical trials did not include any HRQL instruments.

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms

used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

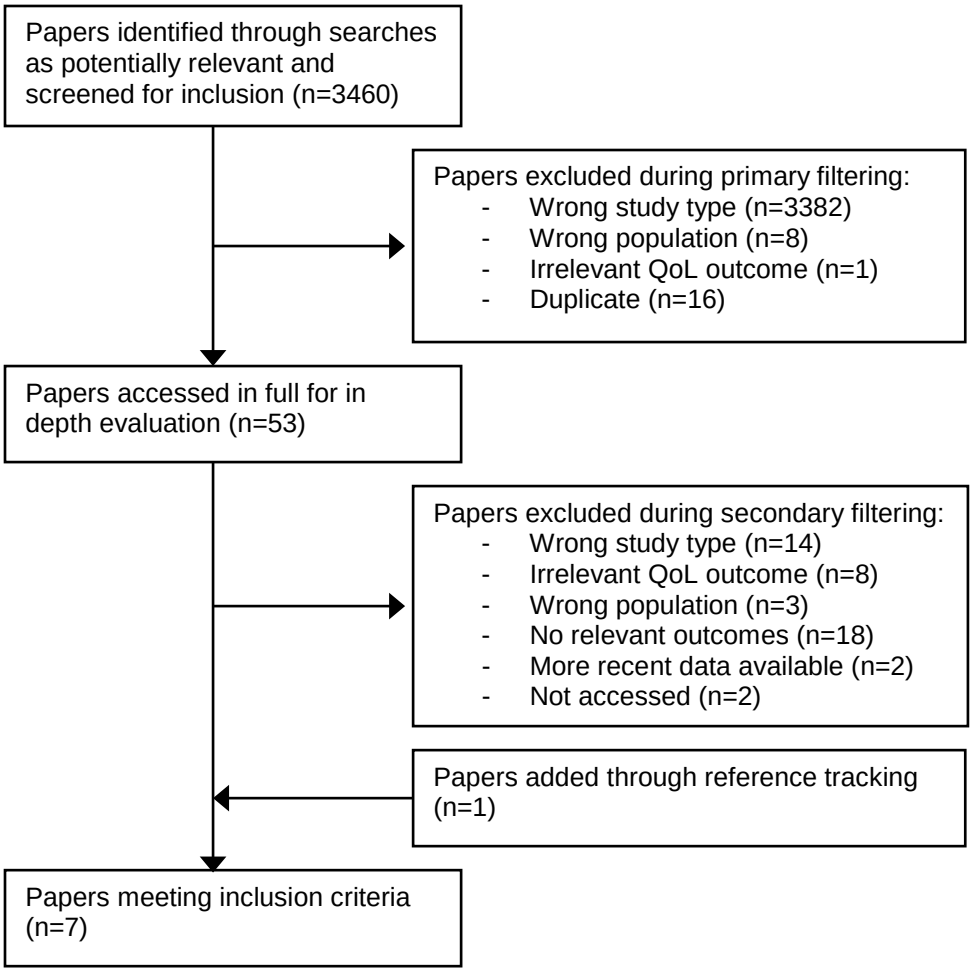
Health related quality of life studies were identified based upon the search results from the economic search detailed in section 7.1.1.

7.4.6 Provide details of the studies in which HRQL is measured.

Identification of Relevant Studies

As illustrated in Figure 30, the majority of the papers initially identified failed to meet the inclusion criteria. The reason for the exclusion in primary filtering of most of the articles was that they were the wrong type of study. One additional paper was added as a result of reference searching. This gave eight studies that met all the inclusion criteria after both primary and secondary filtering. These studies are reviewed below.

Figure 30: Identification of HRQL studies relevant to the decision problem



HRQL, health-related quality of life.

Overview of the relevant studies

Seven studies are included which report relevant utility values. Three of these studies directly measure utilities. Khanna et al measure SF-36 before kyphoplasty and at the last follow-up visit after kyphoplasty in patients with multiple myeloma.[125] The study by van Agthoven et al is a cost-utility analysis also reporting utilities for patients having intensive chemotherapy alone and for patients treated with myeloablative treatment.[126] This study measures quality of life in previously untreated patients. This is not the required population for this review. However, because all the included studies that report secondary utility data use van Agthoven et al as their source, this study has been included.

The remaining five studies are cost-effectiveness analyses, reporting mainly utilities presented by van Agthoven et al.

Results

Table 50 provides the key characteristics of the studies included. appendix K presents the results of the included studies as well as information on methods used.

Table 50: Characteristics of the utilities and HRQL studies included

Reference	Location	Population	Study type	Utilities included
Brown, 2013[127]	UK	rrMM with one prior therapy	Secondary: Cost-effectiveness paper primarily using estimates from van Agthoven	Complete response, partial response, stable disease, progressive disease and utility decrements for adverse events
Felix, 2012[128]	Portugal	rrMM with one or more prior treatments	Secondary: Cost-effectiveness study using estimates from van Agthoven	Stable disease and progressive disease
Fragoulakis, 2013[129]	Greece	rrMM	Secondary: Cost-effectiveness paper using estimates from van Agthoven	Non-responders and all other response levels.
Hornberger, 2010[130]	Sweden	rrMM	Secondary: Cost-effectiveness paper using estimates from van Agthoven	Prior to relapse and after relapse
Khanna, 2006[125]	US	Patients with vertebral compression fractures with osteoporosis or multiple myeloma	Primary: HRQL outcomes study	SF-36 measured before and after kyphoplasty (can be mapped to EQ-5D using domain scores)
Möller, 2011[131]	Norway	rrMM	Secondary: Cost-effectiveness paper using estimates from van Agthoven	Response to treatment and progressive disease / no response
van Agthoven, 2004[126]	Netherlands	Previously untreated multiple myeloma*	Primary: Cost-effectiveness study also reporting outcomes from HRQL outcomes study	EQ-5D using UK tariff: intensive chemotherapy alone and myeloablative treatment based upon time after randomisation

* included as referenced by rrMM studies.
HRQL; health-related quality of life; rrMM: relapsed or refractory multiple myeloma.

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Not applicable.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

Individuals with multiple myeloma find themselves at a heightened risk of various disease related adverse events including hypercalcaemia and anaemia. Toxicities associated with active treatment might also increase the likelihood of experiencing certain events, such as neutropenia, peripheral neuropathy and thrombocytopenia.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

As only one paper presenting health related quality of life for multiple myeloma alone was identified utilities from this source have been used within the model for patients pre and post progression.[126] Utilities have been applied in the same manner as within the model submitted for TA171. The van Agthoven paper presents EQ-5D utilities using a UK tariff and is therefore in line with the reference case.

Adverse event utility decrements are included in the cost-effectiveness analysis, based upon a recent cost-effectiveness analysis identified as part of the search for HRQL information.[127] These are applied on a per-cycle basis as one utility decrement for patients on treatment, or for patients on Len/Dex as a third-line treatment.

The resulting utility decrement per model cycle spent on treatment, accounting for the HRQL impact of adverse events, are:

- Len/Dex: 0.013
- Bortezomib: 0.033
- Bendamustine or chemotherapy agents: 0.025

Table 51: Summary of quality-of-life values for cost-effectiveness analysis

Variable	Value	CI (distribution)	Reference in submission	Justification
Utility value: pre-progression	0.810	0.63 to 0.94 (beta*)		van Agthoven et al, 2004[126]
Utility value: pre-progression after 2 years	0.770	0.60 to 0.90 (beta*)		van Agthoven et al, 2004
Utility value: post-progression	0.640	0.51 to 0.76 (beta*)		van Agthoven et al, 2004
Utility decrement associated with:				
Anaemia	0.310	0.196 to 0.437 (beta**)	Section 7.4.8	Only decrement obtained through systematic search. Brown et al, 2013[127]
Hypercalcaemia	0.000	Not included in SA	Section 7.4.8	Only decrement obtained through systematic search. Brown et al, 2013
Pneumonia	0.190	0.121 to 0.270 (beta**)	Section 7.4.8	Only decrement obtained through systematic search. Brown et al, 2013
Thrombocytopenia	0.310	0.196 to 0.437 (beta**)	Section 7.4.8	Only decrement obtained through systematic search. Brown et al, 2013
Neutropenia	0.145	0.093 to 0.206 (beta**)	Section 7.4.8	Only decrement obtained through systematic search. Brown et al, 2013
Diarrhoea	0.000	Not included in SA	Section 7.4.8	Only decrement obtained through systematic search. Brown et al, 2013
Constipation	0.000	Not included in SA	Section 7.4.8	Only decrement obtained through systematic search. Brown et al, 2013
Peripheral neuropathy	0.065	0.042 to 0.093 (beta**)	Section 7.4.8	Only decrement obtained through systematic search. Coffey et al, 2002[132]
Deep vein thrombosis	0.150	0.096 to 0.213 (beta**)	Section 7.4.8	Only decrement obtained through systematic search. Brown et al, 2013

CI, confidence interval.
* Standard error 10% of the mean; ** Standard error 20% of the mean.

Additionally, within the model utility values are reweighted based upon patient age and standard UK EQ-5D scores[133], as described in section 7.4.14.

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide details[5]:

We did not specifically undertake any clinical expert validation exercise for utility values. The utility values used in this submission are taken from van Agthoven (2004), and have been widely used and referenced in other submissions including NICE TA 171 and TA 228 (see section 7.4.6).[3, 14]

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

In the pre-progression health states, most patients are in receipt of second-line treatment – their initial therapy in this analysis. Some patients discontinue treatment (determined by the TTF model) prior to progression, but the majority of patients discontinue upon progression.

Utility in the pre-progression health state varies over time. In line with van Agthoven et al (2004) and NICE technology appraisals TA171 and TA228, patients who remain progression-free after two years have a slightly reduced utility weight (from 0.81 to 0.77). [3, 14, 126] Patients are also subject to utility decrements associated with treatment-emergent adverse events while on treatment.

Patients with progressive disease experience a utility weight of 0.64. This reflects an increased debilitation associated with the advancement of multiple myeloma. Additionally, the increased monitoring frequency described in section 7.5.6 for progressed patients will present more of a burden to patients, and patients may feel concerned and anxious following the failure of second-line therapy.

[5] 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.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Not applicable.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Quality of life was modelled based upon the model health states.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Three utility values are used to model utility change over time. The pre-progression utility value is 0.81, but if a patient is pre-progression after 2 years this becomes 0.77. The utility value for progressive disease patients is 0.64.[126]

The above utility values are adjusted by an age-dependent factor to reflect decreased utility with age, based upon published UK EQ-5D values.[133] Patients are aged 62 years at the start of the model, which is associated with a multiplicative age-weighting factor of 1. This factor is applied to all utility values until the age of 65, at which point the age-dependent weighting factor becomes 0.975. This factor remains until the age of 74, with all utilities reduced by 2.5%. At 75 years and above the age-dependent weighting factor is 0.913.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Not applicable.

7.5 Resource identification, measurement and valuation

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

The expected HRG coding of best supportive care for multiple myeloma is SA17F – 'Malignant disorders of lymphatic or haematological systems, without CC'. The relevant PbR tariff for 2012/13 and NHS Reference Cost for 2011/12 is found on the Department of Health website.[21, 134] In practice coding may vary between providers.

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

Lenalidomide has been costed based upon the prices reported in the British National Formulary 65.[19] Costs relating to the monitoring of patients and management of adverse events have been estimated using NHS reference costs (2011-12),[134] PSSRU and available literature where tariff costs were not available.[3, 24, 135]

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources.

Resource use and costing studies were identified based upon the search results from the economic search detailed in section 7.1.1.

Table 52 presents the key characteristics of the studies included. appendix L provides the results of the 3 studies as well as information on methods used.

Figure 31: Identification of cost and resource use studies relevant to the decision problem

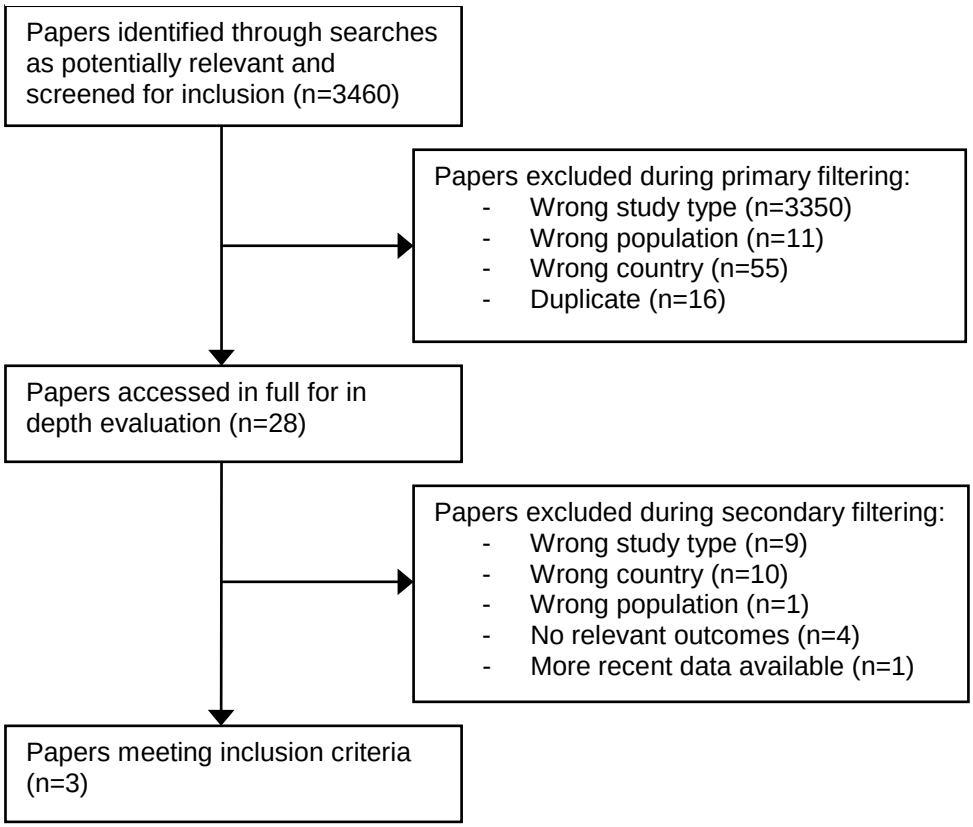


Table 52: Characteristics of the costs and resource use studies identified

Reference	Location	Population	Study type	Resource use and costs included
Brown, 2013[127]	UK	rrMM with one prior therapy	Cost-effectiveness analysis	Costs of treatment and adverse events
Bruce, 1999[136]	England and Wales	multiple myeloma (including rrMM)	Cost analysis	Resource use and costs of standard care, adverse events costs
Popat, 2011[137]	UK	rrMM	Cost analysis	Drug costs

rrMM, relapsed or refractory multiple myeloma.

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide details[6]:

No clinical expert validation exercise was undertaken to elicit input on resource utilisation in the model. The values were directly included from available published literature and previous NICE HTA submissions in multiple myeloma. However, at an advisory board meeting (Celgene Ltd ; 20th June 2013, Golin Harris Offices, London), attended by 11 clinical experts, and where an attempt to estimate actual values for resource utilisation was attempted, experts highlighted that the line of therapy does not predict resource utilisation. This validates the model assumption of resource use being dependent on whether a patient has experienced disease progression or not (section 7.5.6). These resource use inputs replicate those used in NICE technology appraisals 171 and 228.[3, 14]
Further, the clinical experts established that resource use associated with terminal hospital care is likely to be required in 20% of patients. This assumption is included in the cost-effectiveness model and is discussed in further detail in section 7.5.8.

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

[6] 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.

Table 53: Unit costs associated with the technology in the economic model

Items	Lenalidomide/dexamethasone	Bortezomib	Ref. in submission
Technology cost	£3,772.88 Weighted average pack cost Dexamethasone cost: £0.02 per mg	£762.38 Vial list price (BNF65) (Note: a 15% price discount for 2nd line bortezomib is applied as a scenario analysis[138]0	7.5.6
Concomitant G-CSF & administration	Vial cost of £52.70, given to 27% of patients daily for 1 week	N/A	7.5.6
Administration cost	£161.85 Cost for first administration only	£199.83 Cost applied for every administration	7.5.6
Monitoring and routine test costs	£3.21 – £123.71 Unit costs depending on the reason for visit Initial increased monitoring phase of weekly visits applied as per SPC	£3.21 – £123.71 Unit costs depending on the reason for visit	7.5.6
Transport	Unit cost of £12.78, required for 50% of patients to administration appointments		7.5.6
Terminal care	Unit cost of £6177, required for 20% of patients prior to death		7.5.8
AEs: Primary care	£36.00 Unit cost: 11.7 minute contact including direct staff costs, excluding qualification costs, applied to proportion of AEs treated in this setting		7.5.7
AEs: Inpatient setting	£128.00 – £159.56 Unit cost dependent on AE, applied to proportion of AEs treated in this setting		7.5.7
AEs: Day case setting	£132.00 – £480.69 Unit cost dependent on AE, applied to proportion of AEs treated in this setting		7.5.7
AEs: Outpatient setting	£463.00 – £1,274.51 Unit cost dependent on AE, applied to proportion of AEs treated in this setting		7.5.7

AE, adverse event, BNF, British National Formulary; G-CSF, granulocyte colony-stimulating factor; SPC, summary of product characteristics.

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

The model health states have been costed in a similar manner to NICE technology appraisals 171 and 228.[3, 14]

Drug Costs

Drug acquisition prices are obtained from the Department of Health Electronic Market Information Tool (eMit), or the British National Formulary (BNF 65). Unit costs are presented in Table 53.[19, 20]

The weight or body surface area of patients was required to calculate the correct dose for some treatments. A published formula is used to estimate body surface area using weight and height from MM-010.[139]

Lenalidomide

The acquisition cost of lenalidomide applied in the model is calculated as a weighted average of daily doses across all patient days in the MM-010 study.

The clinical study protocol allowed for lenalidomide treatment interruptions and subsequent dose reductions. These are incorporated in the model by analysis of the lenalidomide dose that the trial subjects received on each day of the study, ranging from 25mg to 0mg (where 0mg represents a dose interruption). These were aggregated to provide a mean distribution of patients across the available doses at any given time, shown in Table 54. These dose reductions are as per the lenalidomide SPC.

This analysis provides a typical average lenalidomide dose given at any one time, taking into account the potential for dose interruptions and reductions.

Table 54: Proportion of patient days spent on each lenalidomide dose in MM-010

Daily dose of lenalidomide	Dosing reductions experienced	Proportion of patient days spent in receipt of this dose
25mg	0 (starting dose)	43.2%
25mg + G-CSF	1	26.8%
15mg	2	10.5%
10mg	3	5.0%
5mg	4	3.1%
0mg (interruption)	N/A	11.4%

The study protocol states that all lenalidomide patients initiate treatment on the 25mg daily dosing regimen. The first disruption to this regimen sees patients receive G-CSF alongside 25mg lenalidomide, following a dose interruption. The use of concomitant G-CSF is not included in the lenalidomide SPC at an explicit dosing level, but was included in the MM-010 study. Concomitant use of G-CSF is applied in the model by assuming all patients went on to receive 25mg lenalidomide with G-CSF after their first dose interruption.

The mean time between first and second dose interruptions in MM-010 was 38.3% of the total time to second dose interruption. As such it is assumed this proportion of 25mg lenalidomide patients received concomitant G-CSF, and therefore an estimated 26.8% of all lenalidomide patients receive G-CSF in the model. The 300µg vial of G-CSF is included because this is the dose per day, applied for 1 week in patients who require concomitant G-CSF. This dosing regimen was obtained from a Celgene UK Physician Survey conducted 2011-2012 (section 7.3.5).

The resulting weighted average lenalidomide cycle cost is £3,773.

Dexamethasone (for use in combination therapies)

The acquisition cost of dexamethasone applied in the model is based upon its cost per milligram. This was applied to simplify cost calculations, given that the low price of dexamethasone was unlikely to be an important driver of model results.

The proportion of dexamethasone packs purchased were extracted from the cost source as follows[20]:

- 500 x 2mg: 2%
- 100 x 2mg: 21%
- 50 x 2mg: 77%

Based upon the unit costs per pack in Table 55, a weighted average cost per milligram of £0.02 is applied in the model.

Bortezomib

It is understood that there is a patient access scheme in place for bortezomib at first relapse. This scheme is a complex scheme and the level of discount actually provided is unknown. A scenario analysis is included assuming a discount of 15% which is the expected level of discount detailed in the Summary of VELCADE® Response Scheme document.[138]

Table 55: Drug acquisition costs assumed in the base-case model

Therapy	Standard unit	Source	Unit price
Lenalidomide	21 tab pack: 25mg 21 tab pack: 15mg 21 tab pack: 10mg 21 tab pack: 5mg Dose interruption	BNF 65[19]	£4368.00 £3969.00 £3780.00 £3570.00 £0.00
G-CSF	300µg vial	BNF 65	£52.70
Dexamethasone	500 tab pack: 2mg 100 tab pack: 2mg 50 tab pack: 2mg	eMit[20]	£11.97 £3.23 £1.80
Bortezomib	3.5mg vial	BNF 65	£762.38
Bendamustine	100mg vial 25mg vial	BNF 65	£275.81 £69.45
Melphalan	50mg vial 25 tab pack: 2mg	BNF 65	£129.81 £42.88
Prednisone	100 tab pack: 50mg	BNF 65	£89.00
Prednisolone	28 tab pack: 5mg 28 tab pack: 1mg	eMit	£0.30 £0.16
Cyclophosphamide	1g vial 500mg vial 100 tab pack: 50mg	BNF 65	£17.60 £9.20 £20.20
Cisplatin	100mg vial	eMit	£14.10

Therapy	Standard unit	Source	Unit price
	50mg vial		£7.16
Doxorubicin	200mg vial 50mg vial 10mg vial	eMit	£32.38 £4.87 £1.73
Vincristine	2mg vial 1mg vial	eMit	£8.49 £3.42
Etoposide	500mg vial 100mg vial	eMit	£73.29 £22.38

Treatment administration costs

The unit cost of an intravenous treatment administration appointment is £199.83.[21] This is applied at every administration appointment for IV comparator treatments and subsequent treatments. The unit cost of administering an oral therapy is £161.85.[21] This is applied for the first administration of oral therapies only, after which is it assumed that the patient self-administers the oral treatment.

It is assumed that some patients will require transport to their administration appointments. The unit cost of transport was obtained from NHS reference costs and uplifted to current prices using the Hospital and Community Health Services (HCHS) inflation index, to give £12.78.[21, 24] It is assumed that half (50%) of patients will require this transportation for their treatment administration, based upon the Scottish Medicines Consortium submission of Monofer for the treatment of iron deficiency anaemia.[123] Where a treatment requires more than one administration in a single week, the transport cost is applied only once, under the assumption that a patient will remain in hospital for up to a week at a time to receive the required dose.

Monitoring costs

Monitoring frequency is assumed to depend primarily on whether a patient has experienced a disease progression or not. Treatment with lenalidomide is also associated with an increased monitoring requirement in the early treatment phase in line with monitoring requirements within the SPC.

Monitoring by health state

The monitoring appointments and tests included in the model are presented in Table 56. These were selected following their inclusion in NICE technology appraisals 171 and 228.[3, 14] The annual rate of each event per year was taken from TA171 and converted to a per-cycle rate. The annual rates applied to pre-progression patients

are equivalent to the rate for patients in remission on maintenance therapy. The rates applied to post-progression patients are equivalent to the rate for patients experiencing relapse.

The unit cost of a haematologist appointment was obtained from NHS reference costs.[21] The costs for other monitoring tests were taken from the Evidence Review Group model as part of NICE technology appraisal 228, uplifted to current prices using the HCHS inflation index.[13, 24]

Lenalidomide monitoring

Patients who receive lenalidomide require increased monitoring during their initial stages of treatment. In line with the lenalidomide SPC, patients receive a monitoring visit with full blood tests and investigations (presented in Table 56) weekly for the first eight weeks of treatment. The resulting early-treatment monitoring cost for lenalidomide is £206.06 per week (£824.26 per cycle).

If patients discontinue lenalidomide in this time they are assumed to receive monitoring in a frequency equal to patients with progressive disease, since TTF and PFS are highly similar variables.

Table 56: Monitoring frequency and costs

Follow-up / Monitoring item	Annual rate: Pre-progression	Annual rate: Post-progression	Unit cost
Haematologist appointment	12.0	12.0	£123.71
Full blood count	10.7	20.1	£3.21
Biochemistry tests	9.7	17.3	£5.48
Protein electrophoresis	6.7	9.6	£14.73
Immunoglobin tests	6.4	9.7	£44.20
Urinary light chain excretion	2.7	4.9	£14.73

Subsequent Treatment

Third-line therapies

Real-world data from the HMRN in York, UK were used to inform which therapies are given following discontinuation of Len/Dex in the model.[117] These data were used to implement a ‘best supportive care’ (BSC) mix of therapies representing third-line treatment. Any use of thalidomide in the HMRN data was discounted as it would be

unsuitable for this indication. The resulting make-up of third-line treatment is presented in Table 57. In the base case analysis, patients receive this treatment mix at third line following Len/Dex. However, patients on the comparator model arm receive Len/Dex at third line, in line with the existing treatment pathway. Len/Dex given at third line is associated with the same TTF, OS, adverse events and G-CSF use associated with Len/Dex given at second line as the main model intervention.

A scenario analysis is explored whereby patients on the comparator arm receive a third-line treatment mix based upon the real-world data, which is not exclusively lenalidomide but does include some lenalidomide use, shown in Table 57. If the primary comparator is bortezomib, it is assumed that bortezomib is not used again as a third-line therapy.

Based upon the third-line, real-world treatment basket, a weighted average BSC drug acquisition cost is applied. Similarly, weighted average transport and administration costs are included. All other costs are included per cycle as shown in Table 58, for 17.2 weeks as noted in section 7.3.7.

Table 57: Third-line therapy mix included in the economic model

Third-line therapy	BSC treatment mix			
	Len/Dex arm	Base case comparator arm	Following bortezomib	Other 2nd line comparator
Bortezomib	0.0%	0.0%	0.0%	22.2%
Dexamethasone	56.3%	0.0%	31.3%	5.6%
Melphalan	18.8%	0.0%	10.4%	11.1%
Cyclophosphamide	62.5%	0.0%	34.7%	22.2%
Cisplatin	12.5%	0.0%	6.9%	0.0%
Doxorubicin	12.5%	0.0%	6.9%	0.0%
Etoposide	31.3%	0.0%	17.4%	0.0%
Prednisolone	6.3%	0.0%	3.5%	11.1%
Prednisone	6.3%	0.0%	3.5%	0.0%
Lenalidomide	0.0%	100.0%	44.4%	44.4%

BSC, best supportive care.
Columns sum to more than 100% as patients use more than one treatment.

Table 58: Costs associated with third-line therapy included in the economic model

Cost item	Cost per cycle			
	Len/Dex arm	Base case comparator arm	Following bortezomib	Other 2nd line comparator
Drug cost	£70.20	£3,772.88	£1,716.99	£2,592.00
IV administration	£68.63	£0.00	£49.45	£203.00
Transport	£3.06	£0.00	£2.20	£3.25

Patient access scheme

A patient access scheme currently applies to lenalidomide for the treatment of patients with multiple myeloma who have received two or more prior therapies. The scheme sees the drug provided free of charge to the NHS, for patients who remain on treatment for more than 26 cycles (each of 28 days; normally a period of 2 years).

The acquisition cost of lenalidomide is therefore zero beyond this treatment duration for patients receiving treatment at third line.

Fourth-line therapies

After completion of third-line therapy – based upon the TTF model obtained from MM-010 for Len/Dex, or after a period of 17.2 weeks for BSC, patients immediately move on to fourth-line treatment. The therapy mix at fourth line was obtained from the same UK registry data as the third-line BSC mix.[117] In these data, fourth-line treatment lasts for a mean duration of 16.8 weeks. Reported use of thalidomide is omitted and redistributed proportionately across the other therapies as this patient population are likely to be contraindicated to thalidomide treatment.

The resulting fourth-line therapy mix is presented in Table 59. At this stage of therapy the use of lenalidomide is not attributed a different TTF, OS or adverse event profile. The therapy mix is with earlier costs to give a weighted average fourth-line BSC cost per cycle for drug acquisition, administration and transport, as shown in Table 60.

Table 59: Fourth-line therapy mix included in the economic model

Fourth-line therapy	Treatment mix	
	Including thalidomide	Thalidomide use redistributed
Lenalidomide*	42.9%	60.0%
Melphalan	14.3%	20.0%
Cyclophosphamide	14.3%	20.0%
Thalidomide	28.6%	-
*Base case model assumes dexamethasone also given in combination.		

Table 60: Costs associated with fourth-line therapy included in the economic model

Cost Item	Cost per cycle
Drug cost	£2,277.28
IV administration	£0.00
Transport	£0.00

Fourth-line costs are not dependent upon whether the patient received Len/Dex or a comparator therapy at second line, or whether the patient received Len/Dex or not at third line.

Table 61: List of health states and associated costs in the economic model

Health states	Items	Cost per cycle	Reference in submission
Pre-progression (typically on treatment)	Technology	Lenalidomide: £3,773 Dexamethasone (cycles 1-4): £7.76 Dexamethasone (cycles 5+): £2.59 Bortezomib: £4,067.30	7.5.5
	Concomitant G-CSF and administration	With lenalidomide: £473.62	7.5.5
	Monitoring and tests	£153.34	7.5.5
	Administration	Lenalidomide: £161.85 in first cycle only Bortezomib: £1,065.76	7.5.5
	Transport	Lenalidomide: £6.39 in first cycle only Bortezomib: £17.04	7.5.5
	Adverse events	Lenalidomide: £17.11 Bortezomib: £29.26	7.5.7
Post-progression	3rd line treatment	Following lenalidomide: Therapy: £70.20 IV administration: £69.63 Transport: £3.06 Following bortezomib: Therapy: £1,716.99 IV administration: £49.45 Transport: £2.20	7.5.5
	4th line treatment	Therapy: £2,277.28 IV administration: £0.00 Transport : £0.00	7.5.5
	Monitoring and tests	£175.86	
	Adverse events	In receipt of 3rd line lenalidomide: £17.11 Otherwise: £0.00	7.5.7
	Terminal care	£1,235 on death	7.5.8

G-CSF, granulocyte-colony stimulating factor

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Adverse event unit costs applied in the model are provided in appendix M. The unit cost of treating adverse events depends on the setting in which it is treated. Four possible settings are included in the model: inpatient, hospital day case, outpatient, and general practice. The unit cost of treatment in primary care is that of a GP visit.[24] Other costs are obtained from NHS reference costs.[21]

The unit cost of treating an event in each setting is multiplied by the proportion of events treated in each setting, obtained from NICE technology appraisal 171.[140] The resulting weighted average cost is multiplied by the overall proportion of events actively treated.[140] These inputs are provided in appendix M.

The weighted average cost is then multiplied by the adverse event rates presented in section 7.3.1 to give a cost per cycle per adverse event. These are summed to give the following total adverse event costs per cycle:

- Len/Dex: £17.11 per cycle on treatment
- Bortezomib: £29.26 per cycle on treatment
- Bendamustine and chemotherapy agents: £29.74 per cycle on treatment

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

The cost of terminal care is included in the model when patients die. The unit cost of hospice care for a period of 8 weeks is £6,177, which was obtained by inflating values from a King's Fund report to current prices using the HCHS inflation index.[24, 135] As noted in section 7.5.4 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. To account for this the unit cost of

hospice care is reduced to £1,235, which is applied as a lump sum when a patient dies in the model.

7.6 Sensitivity analysis

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The uncertainty around the following structural assumptions has been included within the model:

- **Time horizon:** Results are presented for shorter time horizons of 5, 10, 15 and 20 years.
- **Treatment pathway:** Results are presented in the base case for the treatment pathway with lenalidomide included as a third-line treatment in line with current NICE recommendations. Additional results are presented with the historical mix of best supportive care at third line based upon data from 2007-09 from the HMRN York registry. In the model base case results are presented compared to bortezomib, which has a market share of approximately 76% of treatment following initial bortezomib when treatment with lenalidomide is excluded (section 7.2.3). As scenarios analyses, results are presented comparing to all other comparators listed within the final scope and also to a blended comparator for all second-line treatments based upon current market shares. Finally, scenario analysis is presented where dexamethasone is not assumed be given in combination with the relevant third- and fourth-line treatments.
- **Modelling lenalidomide efficacy:** Results are presented with treatment failure modeled using progression-free survival rather than time to treatment failure (i.e. treatment is assumed to continue until progression rather than until progression or discontinuation due to adverse events as within the clinical trial). Results are also presented using alternative curve fits for OS, PFS and TTF.
- **Modelling comparative efficacy:** Results are presented using alternative literature to estimate comparative efficacy using all of the relevant sources

identified in the systematic literature search (i.e. all alternative papers identified for bortezomib retreatment).

- **Cost of bortezomib:** Results are presented assuming a PAS discount of 15% at second line.[138] A scenario is tested where this applies to all bortezomib patients, although it is likely that fewer patients will benefit from the scheme in practice.[141] As such, a further scenario is presented whereby 55% of bortezomib patients receive the 15% price discount.

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

The following variables were included in sensitivity analysis:

Table 62: List of variables included in sensitivity analysis

Parameter	Distribution	Rationale
Cohort age, % male, % with beta-2 microglobulin <=2.5mg/L, % with bone lesions at baseline and ECOG status	Age - Normal distribution: 95% CI, based on trial data All other variables – Beta distribution: 95% CI, based on trial data	Based upon available trial data
Discount rates	0-5%	As per guidance
Parameters defining lenalidomide OS	Normal distribution: 95% CI, based on trial data	Could not derive Cholesky decomposition (covariance matrix not positive definite) therefore could not use multivariate normal as would be standard
Parameters defining lenalidomide PFS and TTF	Multivariate normal distribution: 95% CI, based on trial data	Based upon available trial data
Comparative efficacy hazards ratios for OS and PFS	Normal distributions for hazard rates for both lenalidomide and comparator based upon 95% CIs then used to estimate hazard ratio, where information not available from the source 95% CI was assumed to be ±20%	Based upon available trial data and published literature evidence

Parameter	Distribution	Rationale
Dosing of lenalidomide, dexamethasone & G-CSF	Dosing of lenalidomide - Beta tree: 95% CI, based on trial data Proportion receiving G-CSF: Beta distribution: 95% CI, based on trial data Dexamethasone dose in combination with lenalidomide: Normal distribution: 95% CI, based on trial data	Based upon available trial data
Medical resource use	Triangular distribution – upper and lower bounds taken from the source or assumed to be ±20% of the mean where not available	Based upon the upper and lower bounds of the data submitted for TA171
Cost of dexamethasone and chemotherapies available via eMIT	Normal distribution: 95% CI, SE taken from eMIT	Based upon available data
Administration, consultation, adverse events, transport and test costs	Gamma distribution: SD 20% of the mean	Consistent with methodology in TA228
Hospice care	Gamma distribution: SD based upon published data	Consistent with methodology in TA228 and based upon available data
Proportion of patients requiring hospice care and transport	Beta distribution: SE 20% of the mean	Assumption
Duration of 3rd and 4th line therapies	Normal distribution: SE 20% of the mean	Assumption
Proportion of patients receiving each 3rd line treatment	Beta distribution based upon published data	Based upon available data
Proportion of patients receiving each 4th line treatment	Beta tree based upon published data	Based upon available data
Utility values	Beta distribution: SE taken from TA171	Based upon available data
Rates of adverse events	Beta distribution: 95% CI taken from trial data	Based upon available data
Utility decrements for adverse events	Beta distribution: SE 20% of the mean	Assumption

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PFS, progression-free survival; G-CSF, granulocyte-colony stimulating factor.

Deterministic sensitivity analysis was undertaken through the production of a tornado diagram (testing the sensitivity of the model to all parameters and ordering them by impact on the incremental net benefit).

Drug costs were not included within the sensitivity analysis, as the majority of these are taken from the BNF and, therefore, were considered not being subject to

uncertainty. The number of monitoring visits required during the initial monitoring period with lenalidomide was not included in sensitivity analysis as this is defined within the SPC and is therefore not subject to uncertainty.

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

Probabilistic sensitivity analysis was undertaken with all parameters included as described in section 7.6.2. Full details of distributions are presented in appendix N.

7.7 Results

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table 63: Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
Median OS lenalidomide	Not evaluable (95% CI lower bound: 2.9 years)*	4.18 years
Median PFS lenalidomide	1.11 years*	1.10 years
Proportion of patients experiencing adverse events	Rates obtained from trial	Rate applied as obtained from trial

CI, confidence interval; OS, overall survival; PFS, progression-free survival.
* presented in subgroup analysis in section 6.5

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Markov traces are provided in appendix O.

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Markov traces are provided in appendix P.

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Table 64: Model outputs by clinical outcomes – lenalidomide

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
Progression-free survival	2.48	1.73	£110,582
Post-progression survival	3.25	1.68	£10,840
Total	5.74	3.42	£121,422
LY, life years; QALY, quality-adjusted life year.			

Table 65: Model outputs by clinical outcomes – bortezomib

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
Progression-free survival	1.18	0.89	£62,513
Post-progression survival	3.85	1.99	£51,226
Total	5.03	2.89	£113,740
LY, life years; QALY, quality-adjusted life year.			

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 66: Summary of QALY gain by health state

Health state	QALY intervention (lenalidomide)	QALY comparator (bortezomib)	Increment	Absolute increment	% absolute increment
Pre-progression	1.73	0.89	0.84	0.84	73.0%
Post-progression	1.68	1.99	-0.31	0.31	27.0%
Total	3.42	2.89	0.53	1.15	100%

QALY, quality-adjusted life year.

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.

Table 67: Summary of costs by health state

Health state	Cost intervention (lenalidomide)	Cost comparator (bortezomib)	Increment	Absolute increment	% absolute increment
Pre-progression	£110,582	£62,513	£48,069	£48,069	54.3%
Post-progression	£10,840	£51,226	-£40,368	£40,368	45.7%
Total	£121,422	£113,740	£7,682	£88,455	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.

Table 68: Summary of predicted resource use by category of cost

Item	Cost intervention (lenalidomide)	Cost comparator (bortezomib)	Increment	Absolute increment	% absolute increment
Technology cost	£104,211	£47,085	£57,126	£57,126	50.0%
Administration & transport cost	£168	£12,535	-£12,367	£12,367	10.8%
Monitoring & test costs	£11,949	£9,604	£2,345	£2,345	2.1%
3rd line therapy cost (inc. admin and transport)	£204	£40,681	-£40,477	£340,477	35.8%
4th line therapy cost (inc. admin and transport)	£3,428	£2,147	£1,280	£1,280	1.1%
Adverse event costs	£420	£619	-£200	£200	0.2%
Terminal care costs	£1,042	£1,067	-£25	£25	0.0%
Total	£121,422	£113,740	£7,682	£114,289	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.

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table 69: Base-case results

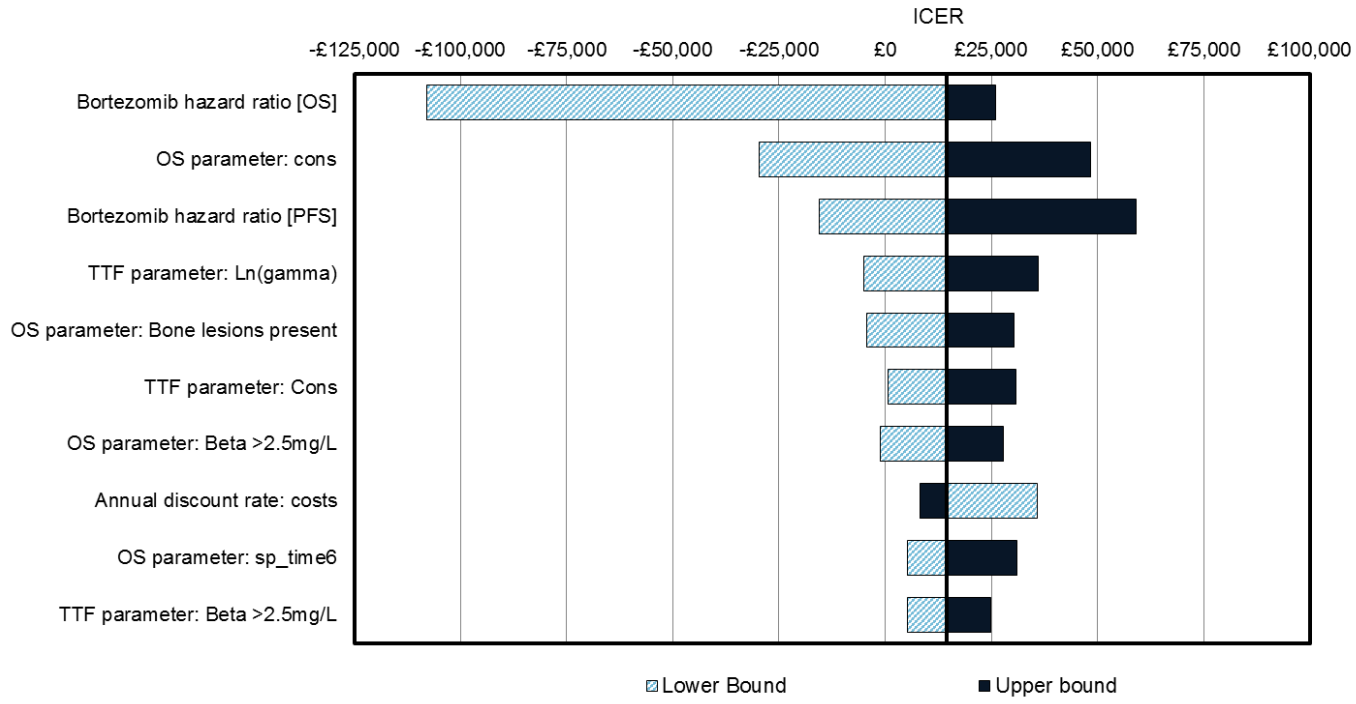
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Bortezomib	113,740	5.03	2.89	-	-	-	-
Lenalidomide	121,422	5.74	3.42	7,682	0.71	0.53	14,535
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Figure 32 shows the 10 parameters to which the ICER is most sensitive when varied individually. Model results are highly sensitive to bortezomib comparative efficacy hazard ratios for OS and PFS relative to Len/Dex. In particular, varying the OS hazard ratio sees the ICER fluctuate from -£107,892 to £26,121. Seven of the parameters shown form part of the estimated regression equations for OS and TTF.

Figure 32: Tornado diagram – top 10 parameters in terms of ICER sensitivity



7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Probabilistic sensitivity analysis was conducted using 1,000 model runs. Results are presented in Table 70. The mean ICER using probabilistic analysis (£13,930 per QALY) was similar to the deterministic ICER (£14,535 per QALY). 73.1% of observations were cost-effective at a £30,000 per QALY threshold. In all cases lenalidomide provided a QALY gain compared to bortezomib.

Table 70: Results from 1,000 PSA simulations

Model outcome	PSA result
Mean incremental costs (SD)	£7,123 (13,648)
Mean incremental QALYs (SD)	0.51 (0.10)
Mean ICER	£13,930
Observations cost-effective at £20,000 threshold	58.6%
Observations cost-effective at £30,000 threshold	73.1%

ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; SD, standard deviation; QALY, quality-adjusted life year.

Figure 33: Cost-effectiveness scatter plot

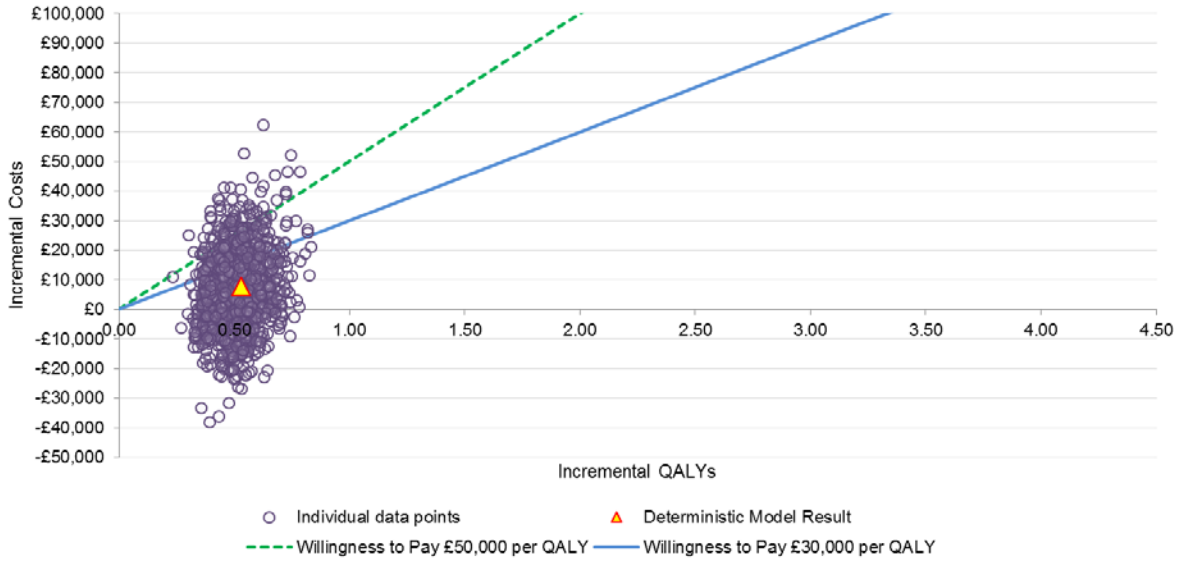


Figure 34: Cost-effectiveness acceptability curve

7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Table 71to Table 75 present the results of scenario analyses. These analyses apply different assumptions to analyse the structural sensitivity of the model.

The base case ICER is £14,535. The ICER is upwardly sensitive to the choice of comparator, whether Len/Dex is used at third line, and the choice of TTF model applied in particular. ICERs versus bendamustine or chemotherapy agents range from £55,621 to £80,180, though these are little used in current clinical practice and

are likely to be even less used in future clinical practice following the recent EMA positive opinion for retreatment with bortezomib in relapsed myeloma as discussed in section 7.2.3.

The ICER impact of different comparative efficacy assumptions varies in either direction, depending on the assumption made. For example, changing the PFS source to Min et al[122] leads to lenalidomide dominating bortezomib. If the White et al paper[42] is used for PFS the ICER increases to £43,331; however, in this paper only 19% of patients had received prior bortezomib. Choosing to use historical best supportive care rather than Len/Dex at third line increases the ICER to £38,330; however, this scenario goes against current NICE recommendations (TA171).

If the log-normal model is selected to TTF the ICER increases to £56,145; however, this is not the optimal parametric model for TTF and provides a relatively poor fit to the data.

Finally, when the bortezomib Patient Access Scheme is included at the expected level of discount stated by the manufacturer (15%) lenalidomide remains cost-effective (ICER £27,898). It is understood that in real life practice the number of patients that receive the discount is 55% of patients, therefore the actual level of discount provided is likely to be lower.[141] Applying a 15% discount to 55% of patients, via an effective price discount of 8.25%, gives an ICER of £21,885.

Table 71: Scenario analysis 1 – time horizon

Parameter	Base Case Assumption	Scenario analysis	ICER
Time horizon	25 years	5 years	Lenalidomide dominates
		10 years	Lenalidomide dominates
		15 years	£4,336
		20 years	£10,736
ICER, incremental cost-effectiveness ratio.			

Table 72: Scenario analysis 2 – type of comparison

Parameter	Base case assumption	Scenario analysis (market share)	ICER
Choice of comparator	Bortezomib retreatment	Bortezomib retreatment/dexamethasone (34%[a])	£14,444
		Bendamustine/prednisolone (6%[b])	£80,108
		Bendamustine/dexamethasone (6%[b])	£55,621
		Melphalan/prednisone (5%[c])	£60,246
		High-dose cyclophosphamide/dexamethasone (5%[c])	£67,660
		Low-dose cyclophosphamide/dexamethasone (5%[c])	£64,345
		Doxorubicin (5%[c])	£66,895
		Vincristine (5%[c])	£64,332
Comparator	Bortezomib retreatment	Blended comparator by market share	£32,462
The use of Len/Dex at third line	As per NICE recommendations (i.e. earlier use of lenalidomide)	As per historical best supportive care (i.e. sub-100% lenalidomide use at third line)	£38,330
Include dexamethasone with 3rd and 4th line treatments where applicable	Yes	No	£14,533

ICER, incremental cost-effectiveness ratio.

a, bortezomib market share includes monotherapy and combination with dexamethasone; b, bendamustine market share includes combination with prednisolone and dexamethasone; c, chemotherapy agents' market shares include all chemotherapies listed

Table 73: Scenario analysis 3 – modelling lenalidomide efficacy

Parameter	Base-case Assumption	Scenario analysis	ICER
Parameter used to model treatment discontinuation	TTF	PFS	£29,077
Curve fit for OS	Piecewise exponential	Weibull (time horizon set to 38 years)	Lenalidomide dominates
Curve fit for PFS	Log-logistic multivariable	Log-normal multivariable	£14,667
Curve fit for TTF	Log-logistic multivariable	Log-normal multivariable	£56,145
Curve fit for PFS and TTF	Log-logistic multivariable	Log-normal multivariable	£56,274

Table 74: Scenario analysis 4 – treatment efficacy assumptions

Parameter	Base-case Assumption	Scenario analysis	ICER
Comparative efficacy of bortezomib	OS from Taverna (2012)[45]	OS from White (2013)[42]	£3,905
	PFS from Taverna (2012)	PFS from Petrucci (2013)[53]	£21,053
		PFS from Hrusovsky (2010)[50]	£10,743
		PFS from Dispenzieri (2010)[80]	£22,288
		PFS from Min (2007)[122]	Lenalidomide dominates
		PFS from White (2013)	£43,331
ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.			

Table 75: Scenario analysis 5 – bortezomib patient access scheme

Parameter	Base-case Assumption	Scenario analysis	ICER
Bortezomib patient access scheme	Not included	15% discount at 2nd line applied for all bortezomib 2nd line patients	£27,898
		15% price discount applied for 55% of bortezomib 2nd line patients	£21,885
ICER, incremental cost-effectiveness ratio.			

7.7.10 What were the main findings of each of the sensitivity analyses?

The mean ICER using probabilistic analysis was similar to the deterministic ICER. 73.1% of probabilistic results observations were cost-effective at a £30,000 per QALY threshold.

The most influential parameters in the model are the hazard ratios for bortezomib PFS and OS relative to Len/Dex and the OS and TTF model parameters. The model is structurally sensitive to the choice of comparator, Len/Dex use at third line and the choice of TTF distribution.

7.7.11 What are the key drivers of the cost-effectiveness results?

The benefits of lenalidomide stem from increased OS and PFS compared to current therapies used following initial treatment with bortezomib (primarily retreatment with bortezomib).

The most influential drivers of model results are the comparative efficacy of bortezomib relative to Len/Dex; the parametric OS model applied; and the parametric time to treatment failure model applied, which determines second-line treatment duration.

For the majority of potential inputs lenalidomide remains cost-effective when compared to bortezomib retreatment. The ICER is £32,462 when compared to a blended comparator of all treatments currently used according to their market shares.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Consistency with previous appraisals of multiple myeloma and published literature

The methodology used within this appraisal and results in terms of OS at second line are generally consistent with the SHTAC model described within TA228.

- OS post treatment in TA228: 3.28 years to 5.74 years
- OS at second line in this submission: 5.74 years lenalidomide and 4.92 years bortezomib retreatment

The estimated life years are, however, high compared to available registry data from 2007 – 2009 for non-transplant patients which predicted an OS of 1.3 years and PFS of 0.7 years.[7] This is to be expected as the registry estimates are impacted by lack of accounting for censoring.

The approach to costing and total costs predicted are comparable to the analysis presented by Bruce et al.[136] Cost for disease management from first relapse to death of £11,738 (inflated to 2012 values £19,329) versus modeled £24,793 for combined cost of administration, transport, monitoring & tests and terminal care (for bortezomib retreatment).

[7] It should be noted that the largest observed analysis time is censored in these analyses, therefore the mean is underestimated

Expert validation

The model approach and inputs have been validated by up to 11 key opinion leaders as reported in sections 7.3.5 and 7.5.4 (some inputs were validated by 11 others were validated by 5) within multiple myeloma. These experts were selected as key opinion leaders practicing in the UK. The experts were asked to validate:

- The treatment pathway following initial treatment with bortezomib and the treatments currently used at second and third line
- Resource use and terminal care costs

Comparability with UK population

The demographics of the UK population in the trial are generally comparable to all patients treated at second line. Compared to the York registry data (for all lines of treatment in 2007-2009) patients within the trial were generally younger at diagnosis (registry mean age at diagnosis is 71.4).

Table 76: Comparison of UK population to MM-010

Parameter	MM-010 2nd line patients lenalidomide (n=56)	UK 2nd line patients lenalidomide (n=7)
% Male	37 (66.0%)	5 (71.4%)
Mean age at diagnosis (years)	60.9	61.1
Duration of melanoma (years)	2.7	2.2
Baseline multiple myeloma stage		
I	3 (5.4%)	1 (14.2%)
III	15 (26.8%)	4 (57.1%)
III	38 (67.9%)	2 (28.6%)
ECOG performance status		
0	27 (48.2%)	4 (57.1%)
1	16 (28.6%)	3 (42.9%)
2	10 (17.9%)	0 (0%)
Unknown	3 (5.4%)	0 (0%)
% with bone lesions present	44 (78.6%)	2 (28.6%)
Baseline beta-2 microglobulin	3.6	3.9
Previously treated with HDT/SCT	38 (67.9%)	3 (42.8%)

ECOG, Eastern Cooperative Oncology Group; HDT, high-dose therapy; SCT, stem cell transplant

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.

7.9 Subgroup analysis

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

No analysis of subgroups was undertaken in this submission.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

No analysis of subgroups was undertaken in this submission.

7.9.3 Please describe how the statistical analysis was undertaken.

No analysis of subgroups was undertaken in this submission.

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

No analysis of subgroups was undertaken in this submission.

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

There were no obvious subgroups and no subgroups were requested for analysis as part of the decision problem.

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

To our knowledge this is the first economic evaluation comparing Len/Dex with bortezomib following one prior treatment regimen. Brown et al report a cost-effectiveness analysis of second-line Len/Dex relative to dexamethasone monotherapy.[127] The outcomes for the Len/Dex arm are consistent with those in the present evaluation in terms of life years and QALYs. Additionally, the acquisition cost of lenalidomide is the main cost driver in both evaluations, and monitoring costs make up a similar proportion of total costs.

The results of this submission should be given more credence than those noted above, as dexamethasone monotherapy does not reflect standard practice in England and Wales and was not included in the final scope for this decision problem. Additionally, an increased level of detail was applied to the inclusion of resource utilisation and costs to provide a more complete picture of the cost outcomes associated with the decision problem.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

The evaluation considers all patients identified in the decision problem.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The primary strength of this evaluation is the use of the MM-010 clinical study to form the lenalidomide evidence base. The evaluation has been structured such that it shares similarities with previous submissions in multiple myeloma, such as TA228 and TA171.

The main weakness of the evaluation is the paucity of evidence with which comparator efficacy and safety outcomes could be included in the model. A literature search was performed to obtain estimates of the comparative efficacy of bortezomib, bendamustine and chemotherapy agents relative to lenalidomide, as these were not included within MM-010.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

An improved understanding of the efficacy of bortezomib, bendamustine and chemotherapy agents in this patient group would enhance the robustness of the model.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The incidence of myeloma in England is 7.1 males per 100,000 and 4.4 females per 100,000 population, and in Wales these figures are 7.4 and 4.1, respectively.[12] These values are presented in Table 77 alongside population statistics and resulting incidence cases of myeloma by gender in England and Wales. The total incidence is 2,368 patients.

Table 77: Incidence of multiple myeloma in England and Wales

Item	Estimate – England	Estimate - Wales	Source
Male population (aged 20+)	18,996,481	1,096,889	NHS Information Centre for Health and Social Care (2010)[11]
Female population (aged 20+)	20,223,021	1,188,486	
Myeloma incidence (per 100,000) – Males	7.1	7.1	Cancer Research UK (2009)[12]
Myeloma incidence (per 100,000) – Females	4.4	4.1	
Total myeloma incidence	1,430	939	Calculation

The NICE costing template for bortezomib in combination with melphalan and prednisolone (VMT) was used to inform the estimated incidence of patients for this submission. The following information was extracted:

- 86.5% 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
- 86.4% of patients are unsuitable for stem-cell transplantation or high-dose chemotherapy
- 15.0% of patients are unable to tolerate thalidomide

Taking these factors into account, a total of 266 incident patients per year are eligible to receive lenalidomide in the present indication.

Growth in the incident population is assumed to occur at a rate of 3.2% per year for men and 1.5% per year for women. This increase is based upon the increase in the mean number of patients per year from 2005-09 and 2006-10, reported by the Office for National Statistics for England.[142]

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

Given the base case analysis of the present economic evaluation, the resource implications are presented based upon the assumption that current treatment is with bortezomib. Additionally, resource implications are presented applying a blended comparator for current treatment, based upon current market share data (section 7.2.2).

8.3 What assumption(s) were made about market share (when relevant)?

The market uptake of lenalidomide is estimated to take the following course, from its current share of 55% through the Cancer Drugs Fund (see section 7.2.2):

- Year 1: 55%
- Year 2: 60%
- Year 3: 63%
- Year 4: 67%
- Year 5: 72%

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

It is not anticipated that lenalidomide will incur other significant costs.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The unit cost of lenalidomide is a weighted average based upon use of the different dosing regimens included in the MM-010 study, described in section 7.2.7. Current list prices for 21-capsule packs were used to calculate this average unit cost as follows: 25mg £4,368; 15mg £3,969; 10mg £3,780; 5mg £3,570. This gives a cost per 28-day cycle of £3,773.

8.6 Were there any estimates of resource savings? If so, what were they?

Resource savings are likely to be made in a reduced requirement for IV administration appointments, blood tests, and monitoring over time.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The annual budget impact is -£1,726,017 in year 1, which translates to a budget impact of -£4,159 per 100,000 population, when current treatment is assumed to be bortezomib for all patients. The annual budget impact in this scenario is -£3,000,652 by year 5, or -£7,230 per 100,000 population.

When a blended comparator based upon market share data is applied, the annual budget impact is -£605,916 in year 1 and -£2,781,688 in year 5.

Table 78: Estimated annual budget impact – current treatment with bortezomib

Year	Incident Patients Treated with Len/Dex	Annual Budget Impact (drug costs only)	Annual Budget Impact (total costs)	Cumulative Budget Impact (total costs)
1	146	£1,285,663	-£1,726,017	-£1,726,017
2	163	£2,611,278	-£3,087,760	-£4,813,777
3	175	£3,744,435	-£3,482,422	-£8,296,199
4	191	£4,810,139	-£3,394,059	-£11,690,258
5	210	£5,862,139	-£3,000,652	-£14,690,910

Table 79: Estimated annual budget impact – current treatment with blended comparator based on market share data

Year	Incident Patients Treated with Len/Dex	Annual Budget Impact (drug costs only)	Annual Budget Impact (total costs)	Cumulative Budget Impact (total costs)
1	146	£2,170,162	-£605,916	-£605,916
2	163	£3,845,712	-£1,431,366	-£2,037,282
3	175	£7,368,080	-£2,083,066	-£4,120,348
4	191	£10,295,992	-£2,537,352	-£6,657,700
5	210	£15,060,089	-£2,781,688	-£9,439,388

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

There may be wider societal benefits due to lenalidomide being an oral therapy, particularly for patients with mobility problems, which have not been included in the above resource impact estimation.

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10 Appendices

10.1 Appendix 1

10.1.1 SPC/IFU, scientific discussion or drafts.

The SPC is provided in the reference pack[1]

10.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter),

- Medline & Medline In-Process & Other Non-Indexed Citations (OVID)
- Embase (OVID)
- Cochrane Library (Wiley Interscience)
    - Cochrane Database of Systematic Reviews: CDSR
    - Cochrane Central Register of Controlled Trials: CCRCT
    - Health Technology Assessment Database: HTA
    - Database of Abstracts of Reviews of Effects: DARE
- CINAHL

10.2.2 The date on which the search was conducted.

All databases were searched on the 14th August 2013.

10.2.3 The date span of the search.

All databases were searched from origin to August 2013. Exact date spans are presented in Table 80.

Table 80: The date span of clinical searches for each database

Database	Date span
Medline	1946 – August 2013
Embase	1974 – August 2013
CCRCT	1898 – August 2013
HTA	1989 – August 2013
DARE	1994 – August 2013
CDSR	1996 – August 2013
CINAHL	1982 – August 2013

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline

1. exp Multiple Myeloma/
2. Plasmacytoma/
3. exp Paraproteinemias/
4. (myeloma$ or plasm?cytom$ or mgus or monoclonal gammopath$ or plasma tumo?r$ or kahler?s disease$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. or/1-4
6. Recurrence/
7. relapse$.mp.
8. refractory.mp.
9. or/6-8
10. 5 and 9
11. rrmm.mp.
12. 10 or 11
13. pomalidomide.mp.
14. (pomalyst or cc-4047 or 3-amino-thalidomide or "pom/dex").af.
15. 13 or 14
16. 12 and 15
17. (bortezomib or velcade).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
18. (bendamustine or levcat).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
19. (carfilzomib or kyprolis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
20. Cyclophosphamide/

21. (cyclophosphamide or cytoxan or endoxan or neosar or procytox or revimmune).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
22. 50-18-0.rn.
23. nsc-26271.af.
24. or/20-23
25. Dexamethasone/
26. (dexamethasone or decadron or dexpak or dexasone or decaject or hexadrol or millicorten).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
27. 50-02-2.rn.
28. or/25-27
29. (lenalidomide or revlimid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
30. (liposomal doxorubicin or caelyx or myocet).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
31. Methylprednisolone/
32. (methylprednisolone or medrol or met?pred or urbason).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
33. 83-43-2.rn.
34. or/31-33
35. Thalidomide/
36. (thalidomid$ or sedoval).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
37. 50-35-1.rn.
38. or/35-37
39. (vorinostat or zolinza).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
40. Melphalan/
41. (me?phalan or sarkolysin$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
42. 148-82-3.rn.
43. or/40-42
44. Prednisone/
45. (prednisone or deltazone or prednisolone).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
46. or/44-45
47. Etoposide/
48. (etoposide or etopophos or vepesid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
49. or/47-48
50. or/17-19,24,28-30,34,38,43,46,49
51. 12 and 50

52. Randomized Controlled Trials as Topic/
53. Randomized Controlled Trial/
54. Random Allocation/
55. Double-Blind Method/
56. Single-Blind Method/
57. Clinical Trial/
58. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv or controlled clinical trial or multicenter study or randomized controlled trial).pt.
59. exp Clinical Trials as Topic/
60. or/52-59
61. (clinical adj trial$).tw.
62. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
63. Placebos/
64. placebo$.tw.
65. randomly allocated.tw.
66. (allocated adj2 random$).tw.
67. or/61-66
68. 60 or 67
69. case report.tw.
70. Letter/
71. Historical Article/
72. or/69-71
73. 68 not 72
74. 51 and 73
75. Meta-Analysis/
76. meta analy$.tw.
77. metaanaly$.tw.
78. meta analysis.pt.
79. (systematic adj (review$1 or overview$1)).tw.
80. exp Review Literature/
81. or/75-80
82. cochrane.ab.
83. embase.ab.
84. (psychlit or psyclit).ab.
85. (psychinfo or psycinfo).ab.
86. (cinahl or cinhal).ab.
87. science citation index.ab.
88. bids.ab.
89. cancerlit.ab.
90. or/82-89
91. reference list$.ab.
92. bibliograph$.ab.
93. hand-search$.ab.
94. relevant journals.ab.
95. manual search$.ab.
96. or/91-95
97. selection criteria.ab.
98. data extraction.ab.
99. 97 or 98
100. review.pt.
101. 99 and 100

102. comment.pt.
103. letter.pt.
104. editorial.pt.
105. animal/
106. human/
107. 105 not (105 and 106)
108. or/102-104,107
109. 81 or 90 or 96 or 101
110. 109 not 108
111. 51 and 110
112. Epidemiologic Studies/
113. exp Case-Control Studies/
114. exp Cohort Studies/
115. case control.tw.
116. (cohort adj (study or studies)).tw.
117. cohort analy$.tw.
118. (follow up adj (study or studies)).tw.
119. (observational adj (study or studies)).tw.
120. (longitudinal or retrospective or cross sectional).tw.
121. Cross-Sectional Studies/
122. or/112-121
123. 51 and 122
124. 74 or 111 or 123
125. limit 124 to humans

Cochrane Library (CDSR, CENTRAL, DARE, HTA)

ID Search

#1 MeSH descriptor: [Multiple Myeloma] explode all trees

#2 MeSH descriptor: [Plasmacytoma] explode all trees

#3 MeSH descriptor: [Paraproteinemias] explode all trees

#4 (myeloma* or plasm?cytom* or mgus or monoclonal gammopath* or plasma tumo?r* or kahler?s disease*):ti,ab,kw (Word variations have been searched)

#5 #1 or #2 or #3 or #4

#6 MeSH descriptor: [Recurrence] explode all trees

#7 relapse* or refractory:ti,ab,kw (Word variations have been searched)

#8 #6 or #7

#9 #5 and #8

#10 rrmm:ti,ab,kw (Word variations have been searched)

#11 #9 or #10

#12 pomalidomide or pomalyst or cc-4047 or 3-amino-thalidomide or "pom/dex":ti,ab,kw (Word variations have been searched)

#13 #11 and #12

#14 bortezomib or velcade:ti,ab,kw (Word variations have been searched)

#15 bendamustine or levcat:ti,ab,kw (Word variations have been searched)

#16 carfilzomib or kyprolis:ti,ab,kw (Word variations have been searched)

#17 MeSH descriptor: [Cyclophosphamide] explode all trees

#18 cyclophosphamide or cytoxan or endoxan or neosar or procytox or revimmune:ti,ab,kw (Word variations have been searched)

#19 50-18-0 or nsc-26271:ti,ab,kw (Word variations have been searched)

#20 #17 or #18 or #19

#21 MeSH descriptor: [Dexamethasone] explode all trees

#22 dexamethasone or decadron or dexpak or dexasone or decaject or hexadrol or millicorten or 50-02-2:ti,ab,kw (Word variations have been searched)

#23 #21 or #22

#24 lenalidomide or revlimid:ti,ab,kw (Word variations have been searched)

#25 liposomal doxorubicin or caelyx or myocet:ti,ab,kw (Word variations have been searched)

#26 MeSH descriptor: [Methylprednisolone] explode all trees

#27 methylprednisolone or medrol or metipred or metypred or met-pred or urbason or 83-43-2:ti,ab,kw (Word variations have been searched)

#28 #26 or #27

#29 MeSH descriptor: [Thalidomide] explode all trees

#30 thalidomid* or sedoval or 50-35-1:ti,ab,kw (Word variations have been searched)

#31 #29 or #30

#32 (vorinostat or zolinza):ti,ab,kw (Word variations have been searched)

#33 MeSH descriptor: [Melphalan] explode all trees

#34 mephalan or melphalan sarkolysin* or 148-82-3:ti,ab,kw (Word variations have been searched)

#35 #33 or #34

#36 MeSH descriptor: [Prednisone] explode all trees

#37 prednisone or deltazone or prednisolone:ti,ab,kw (Word variations have been searched)

#38 #36 or #37

#39 MeSH descriptor: [Etoposide] explode all trees

#40 etoposide or etopophos or vepesid:ti,ab,kw (Word variations have been searched)

#41 #39 or #40

#42 #14 or #15 or #16 or #20 or #23 or #24 or #25 or #28 or #31 or #32 or #35 or #38 or #41

#43 #11 and #42

Embase

1. multiple myeloma/
2. plasmacytoma/
3. exp paraproteinemia/
4. (myeloma* or plasm?cytom* or mgus or monoclonal gammopath* or plasma tumo?r* or kahler?s disease*).tw.
5. or/1-4
6. recurrent disease/
7. (relapse* or refractory).tw.
8. 6 or 7
9. 5 and 8
10. rrmm.tw.
11. 9 or 10
12. pomalidomide/
13. (pomalidomide or pomalyst or cc-4047 or 3-amino-thalidomide or "pom/dex").af.
14. 12 or 13
15. 11 and 14
16. bortezomib/
17. (bortezomib or velcade).tw.
18. bendamustine/
19. (bendamustine or levcat).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
20. carfilzomib/
21. (carfilzomib or kyprolis).tw.
22. cyclophosphamide/
23. (cyclophosphamide or cytoxan or endoxan or neosar or procytox or revimmune).tw.
24. (50-18-0 or nsc-26271).af.
25. dexamethasone/
26. (dexamethasone or decadron or dexpak or dexasone or decaject or hexadrol or millicorten).tw.
27. 50-02-2.af,tw.
28. lenalidomide/
29. (lenalidomide or revlimid).tw.
30. (liposomal doxorubicin or caelyx or myocet).tw.
31. methylprednisolone/
32. (methylprednisolone or medrol or met?pred or urbason).tw.
33. 83-43-2.af.
34. thalidomide/
35. (thalidomid* or sedoval).tw.
36. 50-35-1.af.
37. vorinostat/

38. (vorinostat or zolinza).tw.
39. melphalan/
40. (me?phalan or sarkolysin*).tw.
41. 148-82-3.af,tw.
42. prednisone/
43. (prednisone or deltazone or prednisolone).tw.
44. etoposide/
45. (etoposide or etopophos or vepesid).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
46. or/16-45
47. 11 and 46
48. clinical trial/
49. randomised controlled trial/
50. randomization/
51. single blind procedure/
52. double blind procedure/
53. crossover procedure/
54. placebo/
55. randomi?ed controlled trial$.tw.
56. rct.tw.
57. random allocation.tw.
58. randomly allocated.tw.
59. allocated randomly.tw.
60. (allocated adj2 random).tw.
61. single blind$.tw.
62. double blind$.tw.
63. ((treble or triple) adj blind$).tw.
64. PLACEBO$.tw.
65. prospective study/
66. or/48-65
67. case study/
68. case report.tw.
69. abstract report/ or letter/
70. or/67-69
71. 66 not 70
72. 47 and 71
73. Meta Analysis/
74. ((meta adj analy$) or metaanalys$).tw.
75. (systematic adj (review$1 or overview$1)).tw.
76. or/73-75
77. cancerlit.ab.
78. cochrane.ab.
79. embase.ab.
80. (psychlit or psyclit).ab.
81. (psychinfo or psycinfo).ab.
82. (cinal or cinahl).ab.
83. science citation index.ab.
84. bids.ab.
85. or/77-84
86. reference lists.ab.
87. bibliograph$.ab.

88. hand-search$.ab.
89. manual search$.ab.
90. relevant journals.ab.
91. or/86-90
92. data extraction.ab.
93. selection criteria.ab.
94. 92 or 93
95. review.pt.
96. 94 and 95
97. letter.pt.
98. editorial.pt.
99. animal/
100. human/
101. 99 not (99 and 100)
102. or/97-98,101
103. 76 or 85 or 91 or 96
104. 103 not 102
105. 47 and 104
106. clinical study/
107. case control study/
108. Family study/
109. Longitudinal study/
110. Prospective study/
111. Randomized controlled trials/
112. 110 not 111
113. Cohort analysis/
114. (Cohort adj (study or studies)).mp.
115. (Case control adj (study or studies)).tw.
116. (follow up adj (study or studies)).tw.
117. (observational adj (study or studies)).tw.
118. (epidemiologic$ adj (study or studies)).tw.
119. (cross sectional adj (study or studies)).tw.
120. or/106-109,112-119
121. 47 and 120
122. 72 or 105 or 121
123. limit 122 to human

CINAHL

#	Query
S35	(S30 OR S32 OR S34)

S34	S28 AND S33
S33	TI (epidemiolog* OR stud* case control OR cohort OR follow up OR observational OR longitudinal OR retrospective OR cross sectional OR cross-sectional) OR AB (epidemiolog* OR stud* case control OR cohort OR follow up OR observational OR longitudinal OR retrospective OR cross sectional OR cross-sectional)
S32	(S28 AND S31)
S31	TI (meta-analy* OR metaanalys* OR meta analy* OR review*) OR AB (meta-analy* OR metaanalys* OR meta analy* OR review*)
S30	(S28 AND S29)
S29	TI (random* OR trial* OR blind* OR mask* OR placebo*) OR AB (random* OR trial* OR blind* OR mask* OR placebo*)
S28	(S11 AND S27)
S27	(S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26)
S26	TI (etoposide or etopophos or vepesid) OR AB (etoposide or etopophos or vepesid)
S25	TI (prednisone or deltazone or prednisolone) OR AB (prednisone or deltazone or prednisolone)
S24	TI (mephalan or melphalan or sarkolysin* or 148-82-3) OR AB (mephalan or melphalan or sarkolysin* or 148-82-3)
S23	TI (vorinostat or zolinza) OR AB (vorinostat or zolinza)
S22	TI (thalidomid* or sedoval or 50-35-1) OR AB (thalidomid* or sedoval or 50-35-1)
S21	TI (methylprednisolone or medrol or metypred or met-pred or metipred or urbason or 83-43-2) OR AB (methylprednisolone or medrol or metypred or met-pred or metipred or urbason or 83-43-2)
S20	TI (liposomal doxorubicin or caelyx or myocet) OR AB (liposomal doxorubicin or caelyx or myocet)

S19	TI (lenalidomide or revlimid) OR AB (lenalidomide or revlimid)
S18	TI (dexamethasone or decadron or dexpak or dexasone or decaject or hexadrol or millicorten or 50-02-2) OR AB (dexamethasone or decadron or dexpak or dexasone or decaject or hexadrol or millicorten or 50-02-2)
S17	TI (cyclophosphamide or cytoxan or endoxan or neosar or procytox or revimmune or 50-18-0 or nsc-26271) OR AB (cyclophosphamide or cytoxan or endoxan or neosar or procytox or revimmune or 50-18-0 or nsc-26271)
S16	TI (carfilzomib or kyprolis) OR AB (carfilzomib or kyprolis)
S15	TI (bendamustine or levcat) OR AB (bendamustine or levcat)
S14	TI (bortezomib or velcade) OR AB (bortezomib or velcade)
S13	S11 AND S12
S12	TI (pomalidomide or pomalyst or cc-4047 or 3-amino-thalidomide or "pom/dex") OR (pomalidomide or pomalyst or cc-4047 or 3-amino-thalidomide or "pom/dex")
S11	S9 OR S10
S10	TI rrmm OR AB rrmm
S9	S5 AND S8
S8	S6 OR S7
S7	TI (relapse* or refractory) OR AB (relapse* or refractory)
S6	(MH "Recurrence")
S5	(S1 OR S2 OR S3 OR S4)
S4	TI (myeloma* or plasmacytom* or mgus or monoclonal gammopath* or plasma tumor* or plasma tumour* kahler* disease*) OR AB (myeloma* or plasmacytom* or mgus or monoclonal gammopath* or plasma tumor* or plasma tumour* kahler* disease*)

S3	(MH "Paraproteinemias+")
S2	(MH "Plasmacytoma")
S1	(MH "Multiple Myeloma")

Comparator search strategies

Please note, the following search strategies contain both clinical and cost-effectiveness terms. The clinical-effectiveness elements have been highlighted for clarity.

MEDLINE & EconLit
1. exp Multiple Myeloma/
2. Plasmacytoma/
3. exp Paraproteinemias/
4. (myeloma$ or plasm?cytom$ ormgus or monoclonal gammopath$ or plasma tumo?r$ or kahler?s disease$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. or/1-4 – Search 5 = population
6. pomalidomide.mp.
7. (pomalyst or cc-4047 or 3-amino-thalidomide or "pom/dex").af.
8. 6 or 7
9. (bortezomib or velcade).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
10. (bendamustine or levcat).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
11. (carfilzomib or kyprolis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
12. Cyclophosphamide/
13. (cyclophosphamide or cytoxan or endoxan or neosar or procytox or revimmune).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
14. 50-18-0.rn.
15. nsc-26271.af.
16. or/12-15
17. Dexamethasone/
18. (dexamethasone or decadron or dexpak or dexasone or decaject or hexadrol or millicorten).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
19. 50-02-2.rn.
20. or/17-19
21. (lenalidomide or revlimid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
22. (liposomal doxorubicin or caelyx or myocet).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
23. Methylprednisolone/

24. (methylprednisolone or medrol or met?pred or urbason).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
25. 83-43-2.rn.
26. or/23-25
27. Thalidomide/
28. (thalidomid$ or sedoval).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
29. 50-35-1.rn.
30. or/27-29
31. (vorinostat or zolinza).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
32. Melphalan/
33. (me?phalan or sarkolysin$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
34. 148-82-3.rn.
35. or/32-34
36. Prednisone/
37. (prednisone or deltazone or prednisolone).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
38. or/36-37
39. or/8-11,16,20-22,26,30,35,38
40. Vincristine/
41. (oncovin or leurocristine or VCR).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
42. 40 or 41
43. 39 or 42
44. 5 and 43
45. (201308* or 201307* or 201306* or 201305* or 201304* or 201303*).dc.
46. 44 and 45
47. Meta-Analysis/
48. meta analy$.tw.
49. metaanaly$.tw.
50. meta analysis.pt.
51. (systematic adj (review$1 or overview$1)).tw.
52. exp Review Literature/
53. or/47-52
54. cochrane.ab.
55. embase.ab.
56. (psychlit or psyclit).ab.
57. (psychinfo or psycinfo).ab.
58. (cinahl or cinhal).ab.
59. science citation index.ab.
60. bids.ab.
61. cancerlit.ab.
62. or/54-61
63. reference list$.ab.
64. bibliograph$.ab.
65. hand-search$.ab.
66. relevant journals.ab.
67. manual search$.ab.
68. or/63-67
69. selection criteria.ab.
70. data extraction.ab.
71. 69 or 70

72. review.pt.
73. 71 and 72
74. comment.pt.
75. letter.pt.
76. editorial.pt.
77. animal/
78. human/
79. 77 not (77 and 78)
80. or/74-76,79
81. 53 or 62 or 68 or 73
82. 81 not 80
83. 46 and 82
84. randomized controlled trial.pt.
85. controlled clinical trial.pt.
86. randomized controlled trials/
87. random allocation/
88. double blind method/
89. single blind method/
90. clinical trial.pt.
91. exp Clinical Trial/
92. (clin$ adj25 trial$).ti,ab.
93. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
94. placebos/
95. placebos.ti,ab.
96. random.ti,ab.
97. research design/
98. or/84-97
99. 46 and 98
100. Economics/
101. "costs and cost analysis"/
102. Cost allocation/
103. Cost-benefit analysis/
104. Cost control/
105. cost savings/
106. Cost of illness/
107. Cost sharing/
108. "deductibles and coinsurance"/
109. Health care costs/
110. Direct service costs/
111. Drug costs/
112. Employer health costs/
113. Hospital costs/
114. Health expenditures/
115. Capital expenditures/
116. Value of life/
117. exp economics, hospital/
118. exp economics, medical/
119. Economics, nursing/
120. Economics, pharmaceutical/
121. exp "fees and charges"/
122. exp budgets/
123. (low adj cost).mp.
124. (high adj cost).mp.
125. (health?care adj cost$).mp.
126. (fiscal or funding or financial or finance).tw.
127. (cost adj estimate$).mp.
128. (cost adj variable).mp.
129. (unit adj cost$).mp.
130. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
131. or/100-130

132. 46 and 131
133. or/9-11,16,20-22,26,30,35,38
134. 5 and 133
135. 82 and 134 –Systematic Reviews
136. 98 and 134 –RCTs
137. 131 and 134

EMBASE

1. exp Multiple Myeloma/
2. Plasmacytoma/
3. exp Paraproteinemias/
4. (myeloma$ or plasm?cytom$ ormgus or monoclonal gammopath$ or plasma tumo?r$ or kahler?s disease$).mp.
5. or/1-4 Search 5 = population
6. (bortezomib or velcade).mp.
7. (bendamustine or levcat).mp.
8. (carfilzomib or kyprolis).mp.
9. Cyclophosphamide/
10. (cyclophosphamide or cytoxan or endoxan or neosar or procytox or revimmune).mp.
11. 50-18-0.rn.
12. nsc-26271.af.
13. or/9-12
14. Dexamethasone/
15. (dexamethasone or decadron or dexpak or dexasone or decaject or hexadrol or millicorten).mp.
16. 50-02-2.rn.
17. or/14-16
18. (lenalidomide or revlimid).mp.
19. (liposomal doxorubicin or caelyx or myocet).mp.
20. Methylprednisolone/
21. (methylprednisolone or medrol or met?pred or urbason).mp.
22. 83-43-2.rn.
23. or/20-22
24. Thalidomide/
25. (thalidomid$ or sedoval).mp.
26. 50-35-1.rn.
27. or/24-26
28. (vorinostat or zolinza).mp.
29. Melphalan/
30. (me?phalan or sarkolysin$).mp.
31. 148-82-3.rn.
32. or/29-31
33. Prednisone/
34. (prednisone or deltazone or prednisolone).mp.
35. or/33-34
36. or/6-8,13,17-19,23,27,32,35
37. Vincristine/
38. (oncovin or leurocristine or VCR).mp.
39. 37 or 38
40. 36 or 39 Search 40 = comparators
41. 5 and 40 Search 41 = population + comparators
42. Meta Analysis/
43. ((meta adj analy$) or metaanalys$).tw.

44. (systematic adj (review$1 or overview$1)).tw.
45. or/42-44
46. cancerlit.ab.
47. cochrane.ab.
48. embase.ab.
49. (psychlit or psyclit).ab.
50. (psychinfo or psycinfo).ab.
51. (cinal or cinahl).ab.
52. science citation index.ab.
53. bids.ab.
54. or/46-53
55. reference lists.ab.
56. bibliograph$.ab.
57. hand-search$.ab.
58. manual search$.ab.
59. relevant journals.ab.
60. or/55-59
61. data extraction.ab.
62. selection criteria.ab.
63. 61 or 62
64. review.pt.
65. 63 and 64
66. letter.pt.
67. editorial.pt.
68. animal/
69. human/
70. 68 not (68 and 69)
71. or/66-67,70
72. 45 or 54 or 60 or 65
73. 72 not 71
74. 41 and 73 –Systematic Reviews
75. clinical trial/
76. randomised controlled trial/
77. randomization/
78. single blind procedure/
79. double blind procedure/
80. crossover procedure/
81. placebo/
82. randomi?ed controlled trial$.tw.
83. rct.tw.
84. random allocation.tw.
85. randomly allocated.tw.
86. allocated randomly.tw.
87. (allocated adj2 random).tw.
88. single blind$.tw.
89. double blind$.tw.
90. ((treble or triple) adj blind$).tw.
91. PLACEBO$.tw.
92. prospective study/
93. or/75-92
94. case study/

95. case report.tw.
96. abstract report/ or letter/
97. or/94-96
98. 93 not 97
99. 41 and 98 –RCTs
100. exp SOCIOECONOMICS/
101. exp "Cost Benefit Analysis"/
102. exp "Cost Effectiveness Analysis"/
103. exp "Cost of Illness"/
104. exp "Cost Control"/
105. exp Economic Aspect/
106. exp Financial Management/
107. exp "Health Care Cost"/
108. exp Health Care Financing/
109. exp Health Economics/
110. exp "Hospital Cost"/
111. (financial or fiscal or finance or funding).tw.
112. exp "Cost Minimization Analysis"/
113. (cost adj estimate$).mp.
114. (cost adj variable$).mp.
115. (unit adj cost$).mp.
116. or/100-115
117. 41 and 116

CINAHL

#	Query	Limiters/Expanders	
S74	S26 AND S73	Search modes - Boolean/Phrase	
S73	S71 NOT S72	Search modes - Boolean/Phrase	
S72	AU Anonymous	Search modes - Boolean/Phrase	
S71	S69 NOT S70	Search modes - Boolean/Phrase	
S70	(MH "Animal Studies")	Search modes - Boolean/Phrase	
S69	S65 NOT S68	Search modes - Boolean/Phrase	
S68	S66 OR S67	Search modes - Boolean/Phrase	
S67	PT Letter	Search modes - Boolean/Phrase	
S66	PT Editorial	Search modes - Boolean/Phrase	
S65	S63 OR S64	Search modes - Boolean/Phrase	
S64	cost or costs or economic* or pharmacoeconomic* or price* or pricing*	Search modes - Boolean/Phrase	
S63	S59 OR S62	Search modes -	

		Boolean/Phrase	
S62	S60 OR S61	Search modes - Boolean/Phrase	
S61	(MH "Health Resource Utilization")	Search modes - Boolean/Phrase	
S60	(MH "Health Resource Allocation")	Search modes - Boolean/Phrase	
S59	S53 NOT S58	Search modes - Boolean/Phrase	
S58	S54 OR S55 OR S56 OR S57	Search modes - Boolean/Phrase	
S57	(MH "Business+")	Search modes - Boolean/Phrase	
S56	(MH "Financing, Organized+")	Search modes - Boolean/Phrase	
S55	(MH "Financial Support+")	Search modes - Boolean/Phrase	
S54	(MH "Financial Management+")	Search modes - Boolean/Phrase	
S53	(MH "Economics+")	Search modes - Boolean/Phrase	
S52	S26 AND S51	Search modes - Boolean/Phrase	RCTs
S51	S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50	Search modes - Boolean/Phrase	
S50	TX allocat* random*	Search modes - Boolean/Phrase	
S49	(MH "Quantitative Studies")	Search modes - Boolean/Phrase	
S48	(MH "Placebos")	Search modes - Boolean/Phrase	
S47	TX placebo*	Search modes - Boolean/Phrase	
S46	TX random* allocat*	Search modes - Boolean/Phrase	
S45	(MH "Random Assignment")	Search modes - Boolean/Phrase	
S44	TX randomi* control* trial*	Search modes - Boolean/Phrase	
S43	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	Search modes - Boolean/Phrase	
S42	TX clinic* n1 trial*	Search modes - Boolean/Phrase	
S41	PT Clinical trial	Search modes - Boolean/Phrase	
S40	(MH "Clinical Trials+")	Search modes -	

		Boolean/Phrase	
S39	S5 AND S38	Search modes - Boolean/Phrase	Systematic Reviews
S38	S32 NOT S37	Search modes - Boolean/Phrase	
S37	S33 OR S34 OR S35 OR S36	Search modes - Boolean/Phrase	
S36	(MH "Animals")	Search modes - Boolean/Phrase	
S35	PT editorial	Search modes - Boolean/Phrase	
S34	PT letter	Search modes - Boolean/Phrase	
S33	PT Commentary	Search modes - Boolean/Phrase	
S32	S27 OR S28 OR S29 OR S30 OR S31	Search modes - Boolean/Phrase	
S31	(systematic N1 (review or overview))	Search modes - Boolean/Phrase	
S30	(MH "Literature Review")	Search modes - Boolean/Phrase	
S29	Metaanaly*	Search modes - Boolean/Phrase	
S28	Meta analys*	Search modes - Boolean/Phrase	
S27	(MH "Meta Analysis")	Search modes - Boolean/Phrase	
S26	S5 AND S25	Search modes - Boolean/Phrase	S26 = population + comparator terms
S25	S19 OR S24	Search modes - Boolean/Phrase	S25 = comparator terms
S24	S20 OR S21 OR S22 OR S23	Search modes - Boolean/Phrase	
S23	VCR	Search modes - Boolean/Phrase	
S22	oncovin	Search modes - Boolean/Phrase	
S21	vincristine	Search modes - Boolean/Phrase	
S20	(MH "Vincristine")	Search modes - Boolean/Phrase	
S19	(S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18)	Search modes - Boolean/Phrase	
S18	TI (etoposide or etopophos or vepesid) OR AB (etoposide or etopophos or vepesid)	Search modes - Boolean/Phrase	

S17	TI (prednisone or deltazone or prednisolone) OR AB (prednisone or deltazone or prednisolone)	Search modes - Boolean/Phrase	
S16	TI (mephalan or melphalan or sarkolysin*) OR AB (mephalan or melphalan or sarkolysin*)	Search modes - Boolean/Phrase	
S15	TI (vorinostat or zolinza) OR AB (vorinostat or zolinza)	Search modes - Boolean/Phrase	
S14	TI (thalidomid* or sedoval or 50-35-1) OR AB (thalidomid* or sedoval or 50-35-1)	Search modes - Boolean/Phrase	
S13	TI (methylprednisolone or medrol or metypred or met-pred or metipred or urbason or 83-43-2) OR AB (methylprednisolone or medrol or metypred or met-pred or metipred or urbason or 83-43-2)	Search modes - Boolean/Phrase	
S12	TI (liposomal doxorubicin or caelyx or myocet) OR AB (liposomal doxorubicin or caelyx or myocet)	Search modes - Boolean/Phrase	
S11	TI (lenalidomide or revlimid) OR AB (lenalidomide or revlimid)	Search modes - Boolean/Phrase	
S10	TI (dexamethasone or decadron or dexpak or dexasone or decaject or hexadrol or millicorten or 50-02-2) OR AB (dexamethasone or decadron or dexpak or dexasone or decaject or hexadrol or millicorten or 50-02-2)	Search modes - Boolean/Phrase	
S9	TI (cyclophosphamide or cytoxan or endoxan or neosar or procytox or revimmune or 50-18-0 or nsc-26271) OR AB (cyclophosphamide or cytoxan or endoxan or neosar or procytox or revimmune or 50-18-0 or nsc-26271)	Search modes - Boolean/Phrase	
S8	TI (carfilzomib or kyprolis) OR AB (carfilzomib or kyprolis)	Search modes - Boolean/Phrase	
S7	TI (bendamustine or levcat) OR AB (bendamustine or levcat)	Search modes - Boolean/Phrase	
S6	TI (bortezomib or velcade) OR AB (bortezomib or velcade)	Search modes - Boolean/Phrase	
S5	(S1 OR S2 OR S3 OR S4)	Search modes - Boolean/Phrase	S5 = population terms
S4	TI (myeloma* or plasmacytom* ormgus or monoclonal gammopath* or plasma tumor* or plasma tumour* kahler* disease*) OR AB (myeloma* or plasmacytom* ormgus or monoclonal gammopath* or plasma tumor* or plasma tumour* kahler* disease*)	Search modes - Boolean/Phrase	
S3	(MH "Paraproteinemias+")	Search modes - Boolean/Phrase	
S2	(MH "Plasmacytoma")	Search modes - Boolean/Phrase	
S1	(MH "Multiple Myeloma")	Search modes - Boolean/Phrase	

10.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Additional searches of the following conference proceedings of 2011-2012 were also conducted:

- Conference proceedings of ASH
- Conference proceedings of ASCO
- Conference proceedings of EHA

10.2.6 The inclusion and exclusion criteria.

Details of inclusion and exclusion criteria applied to the combined results of electronic database searches and additional searches are presented inTable 81

Table 81: Eligibility criteria used for study selection

	Inclusion criteria	Exclusion criteria
Population	• Adult patients with relapsed or refractory multiple myeloma (rrMM) with ≥ 1 prior treatment with bortezomib	• Newly diagnosed multiple myeloma or treatment naïve patients • Studies that investigated both newly diagnosed and rrMM, but did not segregated the results • Studies on children and other blood cancer • Studies in which patients had no prior bortezomib
Intervention	• Lenalidomide/dexamethasone	• Lenalidomide monotherapy • Lenalidomide/any other interventions
Comparator	• Bortezomib (Bor) monotherapy • Bortezomib/high-dose dexamethasone (Bor/Dex) • Regimens based on mephalan, vincristine, cyclophosphamide and doxorubicin • Bendamustine	• Any other type of mono-chemotherapy and/ or combination chemotherapy • Stem cell transplantation
Outcomes	• Progression-free survival (PFS) • Overall survival (OS)	• Studies that did not report data on at least one of the outcomes of interested

	Inclusion criteria	Exclusion criteria
	• Overall response rate (ORR) • Best response, including complete response (CR), partial response (PR), and very good partial response (VGPR) Minimal response (MR) if part of an ORR summation. • Time to next treatment (TNT) • Time to progression (TTP) • Adverse events (only grade 3 and 4, or serious AEs) • Health related quality of life (HRQOL)	
Study type	• Randomised and non-randomised controlled trial of ≥ 5 patients • SR/MA of RCTs and non-RCTs	• Letter, secondary analysis with no new/relevant data, expert opinions, commentaries, non-systematic reviews
Language of publication	• English language	• Non -English language
Date	• None for full text publication • 2011-2013: Conference proceedings and SR/MA	

10.2.7 The data abstraction strategy.

Two reviewers independently extracted pre-defined data items from included trials. In case of disagreement between the two reviewers, a third would have extracted data and final results attained by consensus but this was not necessary.

The pre-defined data extraction table, comprised data items related to the basic characteristics of each selected study and study results and was developed based on conventions in to systematic reviews; taking into account information of relevance to the treatment of advanced melanoma, pre-defined outcomes of interest and specific requirements for subsequent quantitative synthesis.

10.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

Table 82: Quality assessment results for MM-009/MM-010

Question	Response
Was randomisation carried out appropriately?	Yes. In trials MM-009 and MM-010, A stratified randomisation list was independently generated before the study was initiated, which randomised the subjects in a 1:1 ratio to either the Len/Dex group or the placebo/Dex group. Randomisation was done centrally using an IVRS. Randomisation was centralized and stratified by three factors: baseline serum beta-2 microglobulin, prior treatment with high-dose chemotherapy or SCT or no prior treatment, and number of prior anti-myeloma regimens.
Was the concealment of treatment allocation adequate?	Yes. MM-009 and MM-010 were double-blind studies. The lenalidomide and placebo capsules were identical in appearance, and the subjects, investigators, other study site personnel, and Celgene personnel who were responsible for the study were blinded to each subject's treatment assignment until the study was unblinded. An IVRS was used and all medication allotments were assigned by the IVRS. The clinical sites enrolled the patients and did so by accessing the central IVRS.
Was a justification of the sample size provided?	The sample size was based on 85% power to detect a hazard ratio of 1.5 for TTP between the two arms (an increase of 6 to 9 months) and 80% power to detect a hazard ratio of 1.5 for OS (an increase of 12-18 months).
Was follow-up adequate?	All patients were followed in the active phase of the study until disease progression or treatment was discontinued for any other reason. Subjects are contacted every 6 months during the follow-up phase.
Were the individuals undertaking the outcomes assessment aware of allocation?	No, all review of outcomes by the adjudication committee were conducted in blinded fashion.
Was the design parallel-group or crossover? Indicate for each crossover trial whether a carryover effect is likely.	It was a parallel-group design. Patients in the placebo/Dex group were only allowed to roll over to receive lenalidomide after disease progression, or cross over to receive Len/Dex after the IDMC had declared the studies could be unblinded. Carry-over effect is not applicable in these two trials.

Question	Response
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	MM-009 took place in the USA and Canada, while MM-010 took place in Europe, Israel and Australia. Specifically, MM-010 included sites in The study was conducted in Australia (6 sites), Austria (1 site), Belgium (2 sites), France (5 sites), Germany (6 sites), Greece (1 site), Ireland (1 site), Israel (3 sites), Italy (6 sites), Poland (3 sites), Spain (6 sites), Switzerland (2 sites), Ukraine (5 sites), and the United Kingdom (3 sites; 2 in London and 1 in Bristol). A total of 15 patients across three UK sites were enrolled into MM-010. These countries are all representative of the clinical practice of lenalidomide use in Western countries and are relevant to that used in the England and Wales. See Table 76 for comparison of second-line patient characterisitcs in the MM-010 trial and UK practice.
How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, and setting.	There is no reason to suspect that the trial patient characteristics and outcomes would differ significantly from those seen in UK practice. However, since MM-009 and MM-010 were initiated, thalidomide and bortezomib have been licensed in Europe for first and second-line treatment, respectively. Therefore the proportion of patients in the UK receiving either of these drugs as prior therapies may be greater in clinical practice than was seen in the trials. In MM-009, 41.8% and 10.7% of patients in the Len/Dex arm had, respectively, received prior treatment with thalidomide and bortezomib. In MM-010, the respective proportions of patients previously treated with these agents were 30.1% and 4.5% in the Len/Dex arm.[40, 41] The patients enrolled in the trials are slightly younger and have a better performance status at baseline than those that might be seen in UK clinical practice. However, the trial data show Len/Dex significantly improves outcomes over Dex regardless of age and performance status.[103, 143]
For pharmaceuticals, what dosage regimens were used in the RCT?	Dosage regimens were the same as those detailed in the SPC.
Were the study groups comparable?	Yes. The demographic and baseline characteristics of the study groups are comparable.
Were the statistical analyses used appropriate?	Yes. The statistical analyses used are considered appropriate. The protocol for both studies, including the statistical methods section, went through a Special Protocol Assessment by FDA and was agreed upon by the agency.

Question	Response
Was an intention-to-treat analysis undertaken?	Yes.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	In the MM-009 and MM-010 trials, patients in the placebo/Dex arm were allowed to cross-over to the Len/Dex arm when there was a documented progression or at unblinding by the IDMC. This cross-over confounded the measurement of OS in favour of the placebo/Dex group in general, and is likely to explain the decreasing difference in OS between the study groups over time. TTP in the placebo/Dex arms is relatively unaffected by the treatment crossover, because most patients had developed PD when the studies were unblinded – 75.0% in MM-009 and 81.1% in MM-010.
FDA, Food and Drug Administration; IDMC, independent data monitoring committee ; IVRS, interactive voice response system; OS, overall survival; PD, progressive disease; SCT, stem cell transplant; SPC, summary of product characteristics TTP, time to progression.	

10.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Not applicable as no indirect or mixed treatment comparison possible based upon the search strategy presented in appendix 2.

10.5 Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

10.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

Not applicable

10.6 Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

The following information should be provided.

10.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process

- The Cochrane Library.

The same search strategy was used to search for non-RCT evidence as presented in appendix 2.

10.7 Appendix 7: Quality assessment of non-RCT(s) in section 6.8 (Non-RCT evidence)

Table 83: Quality assessment results for the 14 non-RCTs on Len/Dex

Trial no. (reference)	MM-021[144]	Kneppers 2010[52]	GEM-PETHEMA[55]	MM-018[56]	Guglielmelli 2011[57]	Delforge 2011[60]	Schwamborn 2011[84]	Klein 2011[62]
Was randomisation carried out appropriately?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Was the concealment of treatment allocation adequate?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Were the groups similar at the outset of the study in terms of prognostic factors?	N/A	N/A	N/A	N/A	No	N/A	N/A	N/A
Were the care providers, participants and outcome assessors blind to treatment allocation?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Were there any unexpected imbalances in drop-outs between groups?	N/A	N/A	N/A	N/A	No	N/A	N/A	N/A
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No	No	No	No	No	No	No	No

Table 84: Quality assessment result for the 14 non RCTs on Len/Dex cont.

Trial no. (reference)	Dimopoulos 2012[63]	Moscetti 2012[65]	Oehrlein 2012[66]	Touzeau 2012[69]	Iida 2010[79]	Dimopoulos 2010b[81]
Was randomisation carried out appropriately?	N/A	N/A	N/A	N/A	NA	No
Was the concealment of treatment allocation adequate?	N/A	N/A	N/A	N/A	NA	No
Were the groups similar at the outset of the study in terms of prognostic factors?	Unclear	N/A	N/A	N/A	NA	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	N/A	N/A	N/A	N/A	N/A	No
Were there any unexpected imbalances in drop-outs between groups?	Unclear	N/A	N/A	N/A	N/A	Not disclosed in publication
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No	No	No	No	No	No

NA, not applicable.

Table 85: Quality assessment results for non-RCT on bendamustine

Trial no. (reference)	Damaj 2012[46]
Was randomisation carried out appropriately?	NA
Was the concealment of treatment allocation adequate?	NA
Were the groups similar at the outset of the study in terms of prognostic factors?	NA
Were the care providers, participants and outcome assessors blind to treatment allocation?	NA
Were there any unexpected imbalances in drop-outs between groups?	NA
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No

NA, not applicable

Table 86: Quality assessment results for non-RCTs on bortezomib treatment

Trial no. (reference)	RETRIEVE[53]	Hrusovsky 2010[50]	Conner 2008[51]	Sood 2009[61]	ECOG E2A02[80]	Taverna 2012[45]
Was randomisation carried out appropriately?	NA	NA	NA	NA	NA	NA
Was the concealment of treatment allocation adequate?	NA	NA	NA	NA	NA	NA
Were the groups similar at the outset of the study in terms of prognostic factors?	NA	NA	NA	NA	NA	NA
Were the care providers, participants and outcome assessors blind to treatment allocation?	NA	NA	NA	NA	NA	NA
Were there any unexpected imbalances in drop-outs between groups?	NA	NA	NA	NA	NA	NA
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No	No	No	No	Yes	No

NA, not applicable

10.8 Appendix 8: Search strategy for section 6.9 (Adverse events)

The following information should be provided.

10.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process

- The Cochrane Library.
- The same search strategy was used to search for adverse events evidence as presented in appendix 2.

10.9 Appendix 9: Quality assessment of adverse event data in section 6.9 (Adverse events)

10.9.1 Please tabulate the quality assessment of each of the non-RCTs identified.

As provided in appendix 3 and 7.

10.10 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

The following information should be provided.

10.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

The following databases were searched:

- CINAHL via EBSCO
- EMBASE via OvidSP
- MEDLINE (including MEDLINE (R) in-Process) via Ovid SP
- NHS EED via the Cochrane Library
- EconLIT via OvidSP

10.10.2 The date on which the search was conducted.

14th August 2013

10.10.3 The date span of the search.

- CINAHL via EBSCO 1982-August 2013
- NHS Economic Evaluations Database via The Cochrane Library 1968-August 2013
- MEDLINE & MEDLINE-In- Process via Ovid SP 1946-August 2013
- EconLit via OvidSP 1961-August 2013
- EMBASE via OvidSP 1974-August 2013

10.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Please note, the following search strategies contain both clinical and cost-effectiveness terms. The cost-effectiveness elements have been highlighted for clarity.

CINAHL

#	Query	Limiters/Expanders	
S74	S26 AND S73	Search modes - Boolean/Phrase	S74 = Population + Comparators + economics filter

S73	S71 NOT S72	Search modes - Boolean/Phrase	S73 = economics filter
S72	AU Anonymous	Search modes - Boolean/Phrase	
S71	S69 NOT S70	Search modes - Boolean/Phrase	
S70	(MH "Animal Studies")	Search modes - Boolean/Phrase	
S69	S65 NOT S68	Search modes - Boolean/Phrase	
S68	S66 OR S67	Search modes - Boolean/Phrase	
S67	PT Letter	Search modes - Boolean/Phrase	
S66	PT Editorial	Search modes - Boolean/Phrase	
S65	S63 OR S64	Search modes - Boolean/Phrase	
S64	cost or costs or economic* or pharmacoeconomic* or price* or pricing*	Search modes - Boolean/Phrase	
S63	S59 OR S62	Search modes - Boolean/Phrase	
S62	S60 OR S61	Search modes - Boolean/Phrase	
S61	(MH "Health Resource Utilization")	Search modes - Boolean/Phrase	
S60	(MH "Health Resource Allocation")	Search modes - Boolean/Phrase	
S59	S53 NOT S58	Search modes - Boolean/Phrase	
S58	S54 OR S55 OR S56 OR S57	Search modes - Boolean/Phrase	
S57	(MH "Business+")	Search modes - Boolean/Phrase	
S56	(MH "Financing, Organized+")	Search modes - Boolean/Phrase	
S55	(MH "Financial Support+")	Search modes - Boolean/Phrase	
S54	(MH "Financial	Search modes -	

	Management+")	Boolean/Phrase	
S53	(MH "Economics+")	Search modes - Boolean/Phrase	
S52	S26 AND S51	Search modes - Boolean/Phrase	
S51	S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50	Search modes - Boolean/Phrase	
S50	TX allocat* random*	Search modes - Boolean/Phrase	
S49	(MH "Quantitative Studies")	Search modes - Boolean/Phrase	
S48	(MH "Placebos")	Search modes - Boolean/Phrase	
S47	TX placebo*	Search modes - Boolean/Phrase	
S46	TX random* allocat*	Search modes - Boolean/Phrase	
S45	(MH "Random Assignment")	Search modes - Boolean/Phrase	
S44	TX randomi* control* trial*	Search modes - Boolean/Phrase	
S43	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	Search modes - Boolean/Phrase	
S42	TX clinic* n1 trial*	Search modes - Boolean/Phrase	
S41	PT Clinical trial	Search modes - Boolean/Phrase	
S40	(MH "Clinical Trials+")	Search modes - Boolean/Phrase	
S39	S5 AND S38	Search modes - Boolean/Phrase	
S38	S32 NOT S37	Search modes - Boolean/Phrase	
S37	S33 OR S34 OR S35 OR	Search modes -	

	S36	Boolean/Phrase	
S36	(MH "Animals")	Search modes - Boolean/Phrase	
S35	PT editorial	Search modes - Boolean/Phrase	
S34	PT letter	Search modes - Boolean/Phrase	
S33	PT Commentary	Search modes - Boolean/Phrase	
S32	S27 OR S28 OR S29 OR S30 OR S31	Search modes - Boolean/Phrase	
S31	(systematic N1 (review or overview))	Search modes - Boolean/Phrase	
S30	(MH "Literature Review")	Search modes - Boolean/Phrase	
S29	Metaanaly*	Search modes - Boolean/Phrase	
S28	Meta analys*	Search modes - Boolean/Phrase	
S27	(MH "Meta Analysis")	Search modes - Boolean/Phrase	
S26	S5 AND S25	Search modes - Boolean/Phrase	S26 = population + comparator terms
S25	S19 OR S24	Search modes - Boolean/Phrase	S25 = comparator terms
S24	S20 OR S21 OR S22 OR S23	Search modes - Boolean/Phrase	
S23	VCR	Search modes - Boolean/Phrase	
S22	oncovin	Search modes - Boolean/Phrase	
S21	vincristine	Search modes - Boolean/Phrase	
S20	(MH "Vincristine")	Search modes - Boolean/Phrase	
S19	(S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18)	Search modes - Boolean/Phrase	
S18	TI (etoposide or	Search modes -	

	etopophos or vepesid) OR AB (etoposide or etopophos or vepesid)	Boolean/Phrase	
S17	TI (prednisone or deltazone or prednisolone) OR AB (prednisone or deltazone or prednisolone)	Search modes - Boolean/Phrase	
S16	TI (mephalan or melphalan or sarkolysin*) OR AB (mephalan or melphalan or sarkolysin*)	Search modes - Boolean/Phrase	
S15	• TI (vorinostat or zolinza) OR AB (vorinostat or zolinza)	Search modes - Boolean/Phrase	
S14	TI (thalidomid* or sedoval or 50-35-1) OR AB (thalidomid* or sedoval or 50-35-1)	Search modes - Boolean/Phrase	
S13	TI (methylprednisolone or medrol or metypred or met-pred or metipred or urbason or 83-43-2) OR AB (methylprednisolone or medrol or metypred or met-pred or metipred or urbason or 83-43-2)	Search modes - Boolean/Phrase	
S12	TI (liposomal doxorubicin or caelyx or myocet) OR AB (liposomal doxorubicin or caelyx or myocet)	Search modes - Boolean/Phrase	
S11	TI (lenalidomide or revlimid) OR AB (lenalidomide or revlimid)	Search modes - Boolean/Phrase	
S10	TI (dexamethasone or decadron or dexpak or dexasone or decaject or hexadrol or millicorten or	Search modes - Boolean/Phrase	

	50-02-2) OR AB (dexamethasone or decadron or dexpak or dexasone or decaject or hexadrol or millicorten or 50-02-2)		
S9	TI (cyclophosphamide or cytoxan or endoxan or neosar or procytox or revimmune or 50-18-0 or nsc-26271) OR AB (cyclophosphamide or cytoxan or endoxan or neosar or procytox or revimmune or 50-18-0 or nsc-26271)	Search modes - Boolean/Phrase	
S8	TI (carfilzomib or kyprolis) OR AB (carfilzomib or kyprolis)	Search modes - Boolean/Phrase	
S7	TI (bendamustine or levcat) OR AB (bendamustine or levcat)	Search modes - Boolean/Phrase	
S6	TI (bortezomib or velcade) OR AB (bortezomib or velcade)	Search modes - Boolean/Phrase	
S5	(S1 OR S2 OR S3 OR S4)	Search modes - Boolean/Phrase	S5 = population terms
S4	TI (myeloma* or plasmacytom* ormgus or monoclonal gammopath* or plasma tumor* or plasma tumour* kahler* disease*) OR AB (myeloma* or plasmacytom* ormgus or monoclonal gammopath* or plasma tumor* or plasma tumour* kahler* disease*)	Search modes - Boolean/Phrase	
S3	(MH "Paraproteinemias+")	Search modes - Boolean/Phrase	
S2	(MH "Plasmacytoma")	Search modes - Boolean/Phrase	
S1	(MH "Multiple Myeloma")	Search modes - Boolean/Phrase	

NHS EED via The Cochrane Library

ID Search
#1 MeSH descriptor: [Multiple Myeloma] explode all trees
#2 MeSH descriptor: [Plasmacytoma] explode all trees
#3 MeSH descriptor: [Paraproteinemias] explode all trees
#4 (myeloma* or plasm?cytom* ormgus or monoclonal gammopath* or plasma tumo?r* or kahler?s disease*)
#5 #1 or #2 or #3 or #4 = population
#6 MeSH descriptor: [Vincristine] explode all trees
#7 oncovin or leurocristine or VCR
#8 bortezomib or velcade
#9 bendamustine or levcat
#10 carfilzomib or kyprolis
#11 MeSH descriptor: [Cyclophosphamide] explode all trees
#12 cyclophosphamide or cytoxan or endoxan or neosar or procytox or revimmune
#13 50-18-0
#14 nsc-26271
#15 MeSH descriptor: [Dexamethasone] explode all trees
#16 dexamethasone or decadron or dexpak or dexasone or decaject or hexadrol or millicorten
#17 50-02-2
#18 lenalidomide or revlimid
#19 liposomal doxorubicin or caelyx or myocet
#20 MeSH descriptor: [Methylprednisolone] explode all trees
#21 methylprednisolone or medrol or met?pred or urbason
#22 83-43-2
#23 MeSH descriptor: [Thalidomide] explode all trees
#24 thalidomid* or sedoval
#25 50-35-1
#26 vorinostat or zolinza
#27 MeSH descriptor: [Melphalan] explode all trees
#28 me?phalan or sarkolysin*
#29 148-82-3
#30 MeSH descriptor: [Prednisone] explode all trees
#31 prednisone or deltazone or prednisolone
#32 {or #6-#31} = comparators
#33 #5 and #31 = population and comparators

EMBASE
1. exp Multiple Myeloma/
2. Plasmacytoma/
3. exp Paraproteinemias/
4. (myeloma$ or plasm?cytom$ ormgus or monoclonal gammopath$ or plasma tumo?r$ or kahler?s disease$).mp.
5. or/1-4 Search 5 = population
6. (bortezomib or velcade).mp.
7. (bendamustine or levcat).mp.
8. (carfilzomib or kyprolis).mp.

9. Cyclophosphamide/
10. (cyclophosphamide or cytoxan or endoxan or neosar or procytox or revimmune).mp.
11. 50-18-0.rn.
12. nsc-26271.af.
13. or/9-12
14. Dexamethasone/
15. (dexamethasone or decadron or dexpak or dexasone or decaject or hexadrol or millicorten).mp.
16. 50-02-2.rn.
17. or/14-16
18. (lenalidomide or revlimid).mp.
19. (liposomal doxorubicin or caelyx or myocet).mp.
20. Methylprednisolone/
21. (methylprednisolone or medrol or met?pred or urbason).mp.
22. 83-43-2.rn.
23. or/20-22
24. Thalidomide/
25. (thalidomid$ or sedoval).mp.
26. 50-35-1.rn.
27. or/24-26
28. (vorinostat or zolinza).mp.
29. Melphalan/
30. (me?phalan or sarkolysin$).mp.
31. 148-82-3.rn.
32. or/29-31
33. Prednisone/
34. (prednisone or deltazone or prednisolone).mp.
35. or/33-34
36. or/6-8,13,17-19,23,27,32,35
37. Vincristine/
38. (oncovin or leurocristine or VCR).mp.
39. 37 or 38
40. 36 or 39 Search 40 = comparators
41. 5 and 40 Search 41 = population + comparators
42. Meta Analysis/
43. ((meta adj analy$) or metaanalys$).tw.
44. (systematic adj (review$1 or overview$1)).tw.
45. or/42-44
46. cancerlit.ab.
47. cochrane.ab.
48. embase.ab.
49. (psychlit or psyclit).ab.
50. (psychinfo or psycinfo).ab.
51. (cinal or cinahl).ab.
52. science citation index.ab.
53. bids.ab.
54. or/46-53
55. reference lists.ab.
56. bibliograph$.ab.

57. hand-search$.ab.
58. manual search$.ab.
59. relevant journals.ab.
60. or/55-59
61. data extraction.ab.
62. selection criteria.ab.
63. 61 or 62
64. review.pt.
65. 63 and 64
66. letter.pt.
67. editorial.pt.
68. animal/
69. human/
70. 68 not (68 and 69)
71. or/66-67,70
72. 45 or 54 or 60 or 65
73. 72 not 71
74. 41 and 73
75. clinical trial/
76. randomised controlled trial/
77. randomization/
78. single blind procedure/
79. double blind procedure/
80. crossover procedure/
81. placebo/
82. randomi?ed controlled trial$.tw.
83. rct.tw.
84. random allocation.tw.
85. randomly allocated.tw.
86. allocated randomly.tw.
87. (allocated adj2 random).tw.
88. single blind$.tw.
89. double blind$.tw.
90. ((treble or triple) adj blind$).tw.
91. PLACEBO$.tw.
92. prospective study/
93. or/75-92
94. case study/
95. case report.tw.
96. abstract report/ or letter/
97. or/94-96
98. 93 not 97
99. 41 and 98
100. exp SOCIOECONOMICS/
101. exp "Cost Benefit Analysis"/
102. exp "Cost Effectiveness Analysis"/
103. exp "Cost of Illness"/
104. exp "Cost Control"/
105. exp Economic Aspect/
106. exp Financial Management/

107. exp "Health Care Cost"/
108. exp Health Care Financing/
109. exp Health Economics/
110. exp "Hospital Cost"/
111. (financial or fiscal or finance or funding).tw.
112. exp "Cost Minimization Analysis"/
113. (cost adj estimate$).mp.
114. (cost adj variable$).mp.
115. (unit adj cost$).mp.
116. or/100-115 – Search 116 = cost-effectiveness filter
117. 41 and 116 Search 117 = population + comparators + cost-effectiveness filter

MEDLINE & EconLit

1. exp Multiple Myeloma/
2. Plasmacytoma/
3. exp Paraproteinemias/
4. (myeloma$ or plasm?cytom$ ormgus or monoclonal gammopath$ or plasma tumo?r$ or kahler?s disease$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. or/1-4 – Search 5 = population
6. pomalidomide.mp.
7. (pomalyst or cc-4047 or 3-amino-thalidomide or "pom/dex").af.
8. 6 or 7
9. (bortezomib or velcade).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
10. (bendamustine or levcat).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
11. (carfilzomib or kyprolis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
12. Cyclophosphamide/
13. (cyclophosphamide or cytoxan or endoxan or neosar or procytox or revimmune).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
14. 50-18-0.rn.
15. nsc-26271.af.
16. or/12-15
17. Dexamethasone/
18. (dexamethasone or decadron or dexpak or dexasone or decaject or hexadrol or millicorten).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
19. 50-02-2.rn.
20. or/17-19

21. (lenalidomide or revlimid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
22. (liposomal doxorubicin or caelyx or myocet).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
23. Methylprednisolone/
24. (methylprednisolone or medrol or met?pred or urbason).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
25. 83-43-2.rn.
26. or/23-25
27. Thalidomide/
28. (thalidomid$ or sedoval).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
29. 50-35-1.rn.
30. or/27-29
31. (vorinostat or zolinza).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
32. Melphalan/
33. (me?phalan or sarkolysin$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
34. 148-82-3.rn.
35. or/32-34
36. Prednisone/
37. (prednisone or deltazone or prednisolone).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
38. or/36-37
39. or/8-11,16,20-22,26,30,35,38
40. Vincristine/
41. (oncovin or leurocristine or VCR).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
42. 40 or 41
43. 39 or 42
44. 5 and 43
45. (201308* or 201307* or 201306* or 201305* or 201304* or 201303*).dc.
46. 44 and 45
47. Meta-Analysis/
48. meta analy$.tw.
49. metaanaly$.tw.
50. meta analysis.pt.
51. (systematic adj (review$1 or overview$1)).tw.
52. exp Review Literature/
53. or/47-52

54. cochrane.ab.
55. embase.ab.
56. (psychlit or psyclit).ab.
57. (psychinfo or psycinfo).ab.
58. (cinahl or cinhal).ab.
59. science citation index.ab.
60. bids.ab.
61. cancerlit.ab.
62. or/54-61
63. reference list$.ab.
64. bibliograph$.ab.
65. hand-search$.ab.
66. relevant journals.ab.
67. manual search$.ab.
68. or/63-67
69. selection criteria.ab.
70. data extraction.ab.
71. 69 or 70
72. review.pt.
73. 71 and 72
74. comment.pt.
75. letter.pt.
76. editorial.pt.
77. animal/
78. human/
79. 77 not (77 and 78)
80. or/74-76,79
81. 53 or 62 or 68 or 73
82. 81 not 80
83. 46 and 82
84. randomized controlled trial.pt.
85. controlled clinical trial.pt.
86. randomized controlled trials/
87. random allocation/
88. double blind method/
89. single blind method/
90. clinical trial.pt.
91. exp Clinical Trial/
92. (clin$ adj25 trial$).ti,ab.
93. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
94. placebos/
95. placebos.ti,ab.
96. random.ti,ab.
97. research design/
98. or/84-97
99. 46 and 98
100. Economics/
101. "costs and cost analysis"/
102. Cost allocation/
103. Cost-benefit analysis/

104. Cost control/
105. cost savings/
106. Cost of illness/
107. Cost sharing/
108. "deductibles and coinsurance"/
109. Health care costs/
110. Direct service costs/
111. Drug costs/
112. Employer health costs/
113. Hospital costs/
114. Health expenditures/
115. Capital expenditures/
116. Value of life/
117. exp economics, hospital/
118. exp economics, medical/
119. Economics, nursing/
120. Economics, pharmaceutical/
121. exp "fees and charges"/
122. exp budgets/
123. (low adj cost).mp.
124. (high adj cost).mp.
125. (health?care adj cost$).mp.
126. (fiscal or funding or financial or finance).tw.
127. (cost adj estimate$).mp.
128. (cost adj variable).mp.
129. (unit adj cost$).mp.
130. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
131. or/100-130 Search 131 = Cost-effectiveness filter
132. or/9-11,16,20-22,26,30,35,38 Search 132 = Comparators
133. 5 and 132 Search 133 = Population + Comparators
134. 131 and 133 Search 134 = Population + Comparators + Cost-effectiveness filter

10.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Additional searches were conducted for relevant abstracts from the:

- ASH conference proceedings 2011-2012
- ASCO conference proceedings 2011-2012
- EHA conference proceedings 2011-2012

These searches were conducted on the 5th April 2013 using search terms for refractory multiple myeloma.

10.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

N/A.

10.12 Appendix 12: Search strategy for section 7.4 (Measurement and valuation of health effects)

The following information should be provided.

10.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.
- Utilities studies were identified from the results identified by the searches presented in appendix 10.

10.12.2 The date on which the search was conducted.

Presented in appendix 10.

10.12.3 The date span of the search.

Presented in appendix 10.

10.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Presented in appendix 10.

10.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Presented in appendix 10.

10.12.6 The inclusion and exclusion criteria.

Inclusion Criteria		
Category	Inclusion Criteria	Rationale
Study Type	Studies reporting utilities or HRQL data	The aim of the review was to identify relevant utilities
Population	Adults with multiple myeloma who had previously had one line of therapy	This is the relevant patient population
Interventions	There was no restriction to intervention	
Outcomes	Any reported measurement in the form of utilities was included. Also utility values mapped from a measure of HRQL or a measure of HRQL that can be mapped using only published information	The aim of the review was to identify relevant utility values
Exclusion criteria		
Category	Exclusion Criteria	Rationale
Publication Type	Letters; editorials; reviews of utility studies (although reference lists of these were be hand-searched)	Primary study articles were required.

10.12.7 The data abstraction strategy.

In order to ensure the published literature was comprehensively reviewed, a wide range of databases was searched. These included: Medline, Embase, Cochrane Library, NHS EED, HTA database, DARE, CINAHL and Econlit, along with subject-specific conference proceedings of proceedings of ASH, ASCO and EHA.

In addition to the formal electronic searches, reference lists of included cost-effectiveness and quality-of-life studies identified were hand searched and scanned for additional publications of relevance to the research question. Having identified studies from a wide range of databases, the titles and abstracts were reviewed in greater detail to assess their relevance for informing the overall decision problem. The population criteria were not restricted to prior bortezomib, as was the case for

the identification of relevant cost effectiveness studies. Additionally, no intervention criteria were included, to widen the pool of results for HRQL studies.

The papers which, from a detailed review of the title and abstract, appeared to meet the inclusion criteria were obtained for a secondary review. This secondary review involved the entire article being assessed according to the inclusion/exclusion criteria.

10.13 Appendix 13: Resource identification, measurement and valuation (section 7.5)

The following information should be provided.

10.13.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.
- Cost and resource use studies were identified from the results identified by the searches presented in appendix 10.

10.13.2 The date on which the search was conducted.

Presented in appendix 10.

10.13.3 The date span of the search.

Presented in appendix 10.

10.13.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Presented in appendix 10.

10.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Presented in appendix 10.

10.13.6 The inclusion and exclusion criteria.

Inclusion Criteria		
Category	Inclusion Criteria	Rationale
Study Type	Studies reporting costs and resource use	The aim of the review was to identify relevant costs and use of resources
Population	Adults with multiple myeloma who had previously had one line of therapy	This is the relevant patient population
Interventions	There was no restriction to intervention	
Outcomes	Studies reporting the resource use and costs associated with the treatment and ongoing management of multiple myeloma	The aim of the review was to identify relevant costs and data about resource use
Country of Study	UK	Costs and use of resources from a UK perspective were required
Exclusion Criteria		
Category	Exclusion Criteria	Rationale
Publication Type	Letters; editorials; reviews of cost and resource use studies (although reference lists of these were being hand-searched)	Primary study articles were required.

10.13.7 The data abstraction strategy.

- In order to ensure the published literature was comprehensively reviewed, a wide range of databases was searched. These included: Medline, Embase, Cochrane Library, NHS EED, HTA database, DARE, CINAHL and Econlit, along with subject-specific conference proceedings of the proceedings of ASH, ASCO and EHA.
- In addition to the formal electronic searches, reference lists of included cost-effectiveness and cost and resource use studies identified were hand searched and scanned for additional publications of relevance to the research question. Having identified studies from a wide range of databases, the titles and abstracts were reviewed in greater detail to assess their relevance for informing the overall decision problem. The population criteria was not restricted to prior bortezomib, as was the case for the identification of relevant cost effectiveness studies. Additionally, no intervention criteria were included, to widen the pool of results for cost and resource use studies.
- The papers which, from a detailed review of the title and abstract, appeared to meet the inclusion criteria were obtained for a secondary review. This secondary review involved the entire article being assessed according to the inclusion/exclusion criteria.

11 Related procedures for evidence submission

11.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licenses for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

11.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during

the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and separately highlight information that is submitted under ‘commercial in confidence’ in turquoise and information submitted under ‘academic in confidence’ in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be ‘blacked out’ from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of ‘academic in confidence’ information. The ‘stripped’ version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE’s website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the ‘stripped’ version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will

restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.