NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lenalidomide for previously untreated multiple myeloma [ID474]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Lenalidomide for previously untreated multiple myeloma [ID474]

Contents:

The following documents were considered by the Committee at a meeting on 1 February 2018:

1. **Pre-Meeting Briefing**

2. **Final Scope and Final Matrix of Consultees and Commentators**

3. **Company submission from Celgene**

4. **Clarification letters**
   - NICE request to the company for clarification on their submission
   - Company response to NICE's request for clarification

5. **Patient group, professional group and NHS organisation submission** from:
   - Leukaemia CARE
   - Myeloma UK
   - UK Myeloma Forum (UKMF)
   - NHS England

   The NCRI-ACP-RCP endorsed the UKMF statement

6. **Expert statements** from:
   - Dr Karthik Ramasamy, Consultant Haematologist, Oxford University Hospitals – clinical expert, nominated by Celgene
   - Dr Matthew Streetly, Consultant Haematologist, Guys and St. Thomas NHS Foundation Trust – clinical expert, nominated by the UKMF

7. **Evidence Review Group report** prepared by **Southampton Health Technology Assessment Group**

   The Evidence Review Group report was updated after the factual accuracy check to correct the errors identified

8. **Evidence Review Group report – factual accuracy check**

After the February 2018 meeting the company replaced their complex Patient Access Scheme with a simple discount. The following documents were considered by the Committee:

9. **The steps to replace the lenalidomide complex patient access scheme (PAS) with a simple discount – March 2019** from Celgene

10. **Evidence Review Group critique of March 2019 document** – prepared by the Peninsular Technology Assessment Group

NICE National Institute for Health and Care Excellence

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

Pre-meeting briefing

Lenalidomide in combination with dexamethasone for previously untreated multiple myeloma [ID474]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

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

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

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Common abbreviations			
AE	adverse event	MID	minimal important difference
AIC	Akaike information criterion	MM	multiple myeloma
AMT	anti-myeloma therapy	MP	melphalan and prednisone
BIC	Bayesian information criterion	MPT	melphalan, prednisone and thalidomide
BOR	bortezomib	MSM	multi-state Markov
CI	confidence interval	MTC	mixed treatment comparison
CTD	cyclophosphamide, thalidomide and dexamethasone	NDMM	newly diagnosed multiple myeloma
CTDa	attenuated cyclophosphamide, thalidomide and dexamethasone	NMA	network meta-analysis
CR	complete response	NR	not reported
CrI	credible interval	ORR	overall response rate
DEX	dexamethasone	OS	overall survival
DOR	duration of response	PANO	panobinostat
ECOG	Eastern Cooperative Oncology Group	PAS	patient access scheme
EFS	event-free survival	PFS	progression-free survival
EMA	European Medicines Agency	PFS 2	progression-free survival 2
EORTC	European Organisation for Research and Treatment of Cancer	PR	partial response
EORTC QLQ-C30	EORTC Quality of Life Questionnaire – Core 30	PSA	probabilistic sensitivity analysis
EORTC QLQ-MY20	EORTC Quality of Life Questionnaire – Multiple Myeloma 20	QALY	quality-adjusted life-year
EQ-5D	5-dimension European Quality of Life questionnaire	QoL	quality of life
FDA	Food and Drugs Administration	RCT	randomised controlled trial
HR	hazard ratio	RDI	relative dose intensity
HRQoL	health-related quality of life	RRMM	relapsed/refractory multiple myeloma
ICER	incremental cost-effectiveness ratio	SAE	serious adverse event
IMWG	International Myeloma Working Group	SmPC	summary of product characteristics
IRAC	Independent Response Adjudication Committee	TEAE	treatment-emergent adverse event
ISS	International Staging System	TTF	time to treatment failure
LEN+DEX	lenalidomide ,low-dose dexamethasone until PD	TTP	time to progression
LY	life-year	TTR	time to response
		VMP	bortezomib, melphalan and prednisone

Multiple myeloma
Disease background

- Bone marrow cancer affecting plasma cells (a type of white blood cell)
- Cancerous plasma cells produce large amounts of an abnormal antibody known as paraprotein, which supress the production of normal blood cells (white, red and platelets). Paraproteins do not have the capacity to fight infection.
- Common symptoms
  - Bone pain, fractures, anaemia, infections, hypercalcaemia
- Characterised by multiple relapses
- Incidence and survival
  - 5,501 people diagnosed in the UK in 2014, that is 2% of all cancer diagnoses
  - 45% of diagnoses in people aged 75 and over (2012 to 2014)
  - 5-year survival rate is approximately 47%

Lenalidomide (Revlimid)

Celgene

Marketing authorisation	Indicated as combination therapy for people with Newly Diagnosed Multiple Myeloma (NDMM) who are not eligible for transplantation
Administration & dose	• Oral, 25 mg/day on days 1–21 of a 28 day cycle. Taken until disease progression or unacceptable toxicity • Contraindications for lenalidomide are the same as thalidomide: pregnancy and hypersensitivity
Mechanism of action	A structural analogue of thalidomide. Has anti-neoplastic, anti-angiogenic, pro-erythropoeitic and immunomodulatory properties.
Cost	New approved complex PAS where cost of lenalidomide is capped at [redacted] cycles (previously 26 cycles) Average cost per course without PAS: £[redacted] Average cost per course with PAS: £[redacted]

Source: Table B.2 (page 15-16), company submission

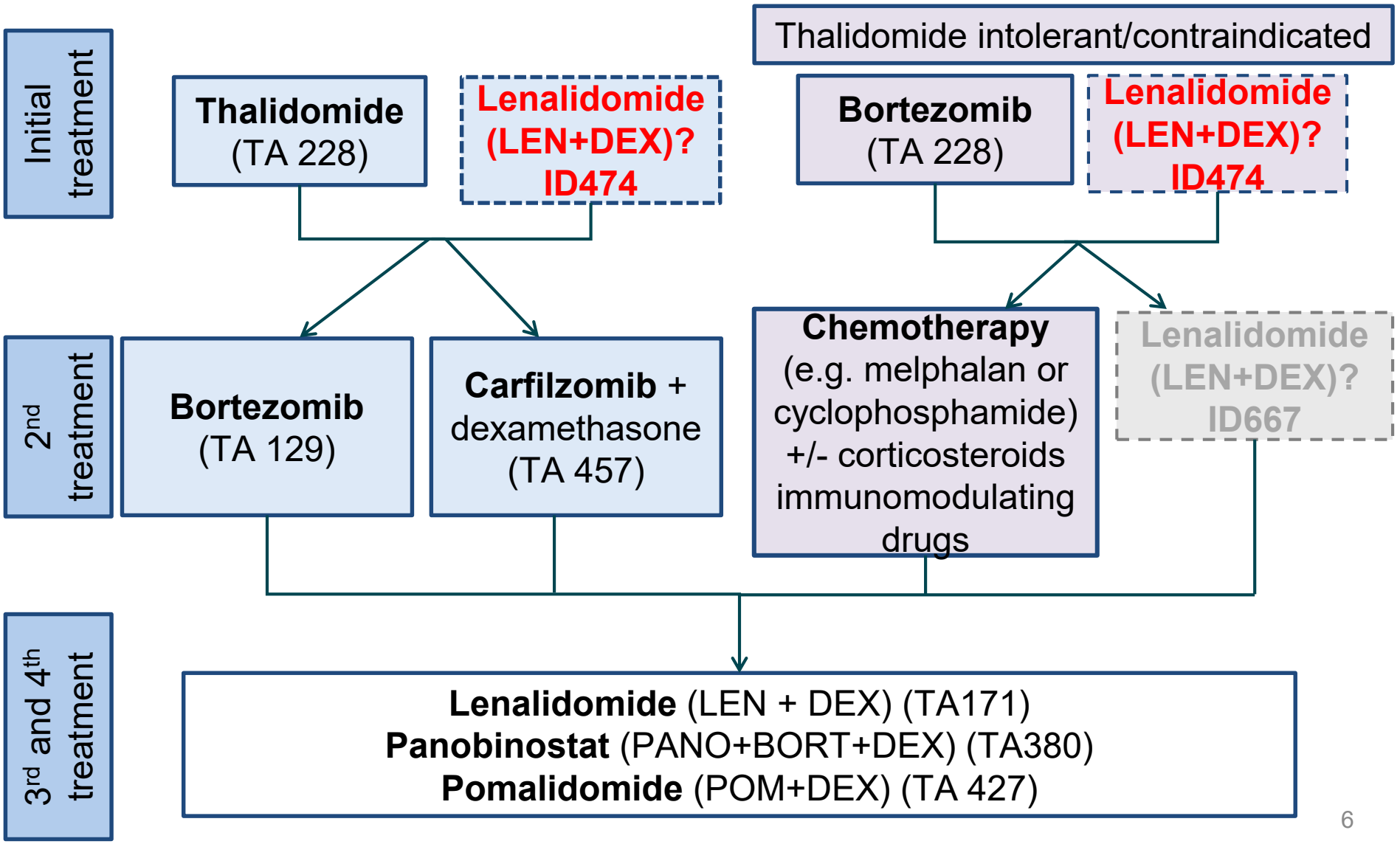
Final Scope

Population	Adults with previously untreated multiple myeloma for whom stem-cell transplantation is considered inappropriate
Intervention	Lenalidomide in combination with dexamethasone
Comparators	• Thalidomide + alkylating agent + corticosteroid If thalidomide intolerant or contraindicated • Bortezomib + alkylating agent + corticosteroid
Outcomes	• overall survival • progression-free survival • response rates • time to next treatment • time to treatment failure • adverse effects of treatment • health-related quality of life.

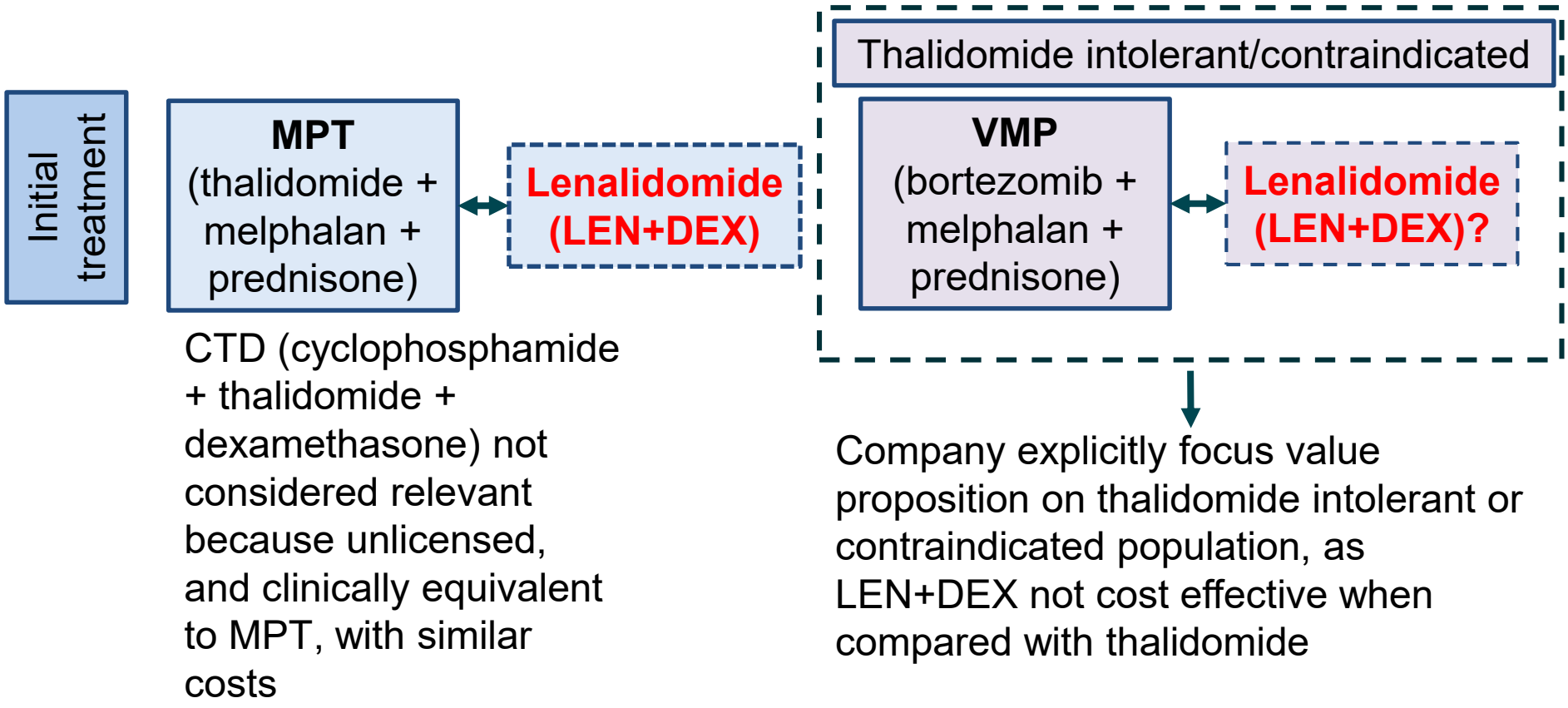
Source: Final scope

Clinical pathway of care

For those who are not eligible for transplantation



Company's decision problem



Subsequent therapies

Company model that people have subsequent treatment or retreatment with thalidomide, bortezomib or lenalidomide based regimes

Company's decision problem
ERG comments

- A meta-analysis published as a conference abstract identified by the ERG indirectly compared MPT with CTD and reported no difference between the 2 in PFS and OS
- Expert advice to the ERG estimates that around 50% of patients may be intolerant or contraindicated to thalidomide. Intolerance is subjective and factors influencing the choice of treatment vary
- Whilst adverse effects of thalidomide can be difficult to tolerate some patients still prefer thalidomide as it is an oral therapy in comparison to bortezomib which is administered either intravenously or subcutaneously
- Cyclophosphamide, bortezomib and dexamethasone (CVD) is an alternative bortezomib-based 1st line treatment used in the UK.
    - The ERG notes that it is unlicensed for 1st line use
    - Searches did not identify any relevant trial evidence that would allow it to be compared to lenalidomide.

Patient expert comments

- Patients and their carers place a very high value on treatments that put their myeloma into remission for as long as possible, prolong their life and allow them to enjoy normal day-to-day life
- Range of symptoms including bone pain, tiredness, unexplained weight loss, frequent and persistent infections etc. These can collectively and individually impact hugely on patients' quality of life
- Unmet need for treatments with a different mechanism of action. Some patients may tolerate a treatment well and others may not
- Lenalidomide may be of particular benefit to people who have peripheral neuropathy (either pre-existing or drug related), as they cannot take thalidomide and are also unlikely to tolerate bortezomib
- Most patients welcome the option of an oral regimen
- Frail and elderly patients, who are more susceptible to side-effects, would benefit particularly from a two drug rather than a three drug combination

Clinical expert comments

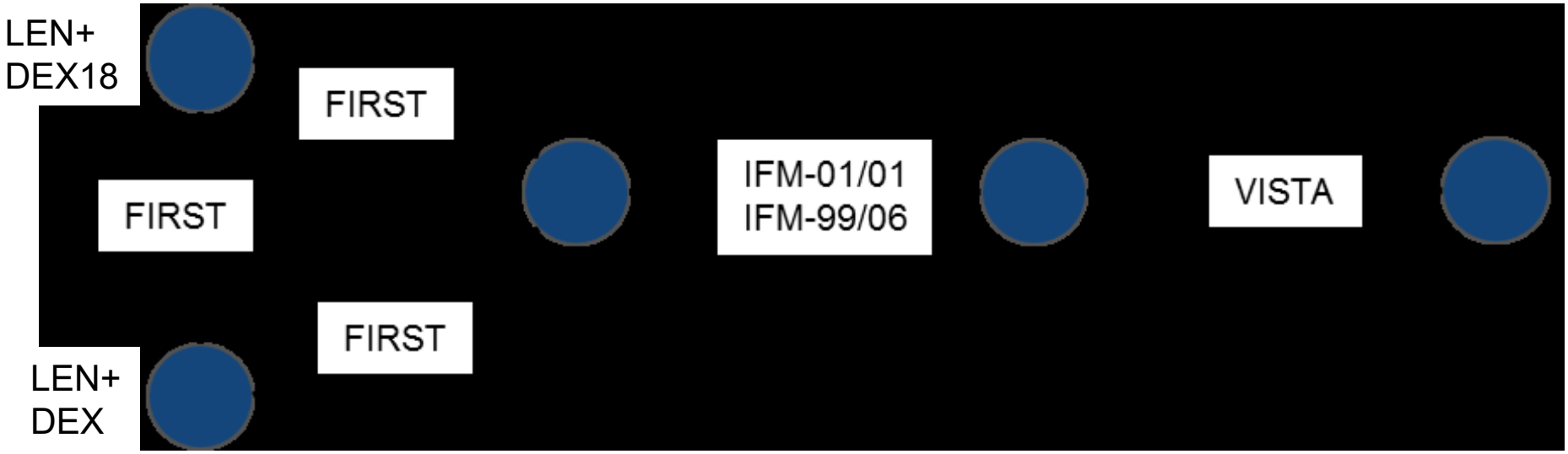
- Generally in the UK for those receiving thalidomide-based treatment, CTD is used in preference to MPT as this was one of the arms of the UK-based Myeloma IX trial that influenced clinical practice significantly
  - MPT is considered relatively equivalent to CTD
- Lenalidomide results in better quality of life compared with CTD/MPT due to much lower rate of peripheral neuropathy
- Quality of life is also likely to be improved due less hospital attendance and ease of administration
- Main concomitant medication required with lenalidomide is the use of aspirin or low molecular weight heparin to reduce the risk of thrombosis (this is also required for thalidomide-based treatments)
- Key benefit of lenalidomide is being able to treat elderly age group and people with neuropathy

Clinical effectiveness evidence

Company submission section 4

Clinical evidence

- FIRST randomised controlled trial (RCT) compares continuous LEN+DEX with LEN+DEX limited to 18 cycles (LEN+DEX18) and with MPT
  - Company state that LEN+DEX limited to 18 cycles is not of relevance to the decision problem for this appraisal
- Further RCTs included so overall survival and progression-free survival of LEN+DEX could be indirectly compared to VMP
- Melphalan and prednisone (MP) included to connect the network



Source: Figure B.14 (page 67), company submission

Clinical evidence
ERG comments

- Evidence for lenalidomide is based on a large international multi-centre RCT (n=1623 patients randomised), included a range of relevant outcomes measures, and had mature results (median follow-up of 67 months)
- No significant differences between age, gender, race or biochemical parameters between treatment arms in the FIRST trial
- All the RCTs in the network are of good methodological quality and have been included in previous NICE appraisals
- However, none of the included trials specifically recruited people who were intolerant or who had contraindications to thalidomide
    - Clinical expert advice to the ERG suggests that results would unlikely to be different in those patients

FIRST
Study methodology

Study design	Multi-center (16 UK sites), randomised, open-label, 3-arm trial
Population	Patients with NDMM aged 65 years or over, or aged under 65 and not a candidate for stem cell transplantation.
Primary outcome	• **Progression-free survival (PFS) per investigator assessment***
Other outcomes specified in the decision problem	• **Overall survival (OS)** • Response rates per investigator assessment • **Time to treatment failure (TTF) per investigator assessment** • Time to next treatment • **Adverse Events** • **Health related quality of life (HRQoL)** using QLQ-C30, QLQ-MY20, and **EQ-5D** questionnaires
Data-cut	All results used in economic model from Jan 2016 data cut PFS, response rate, and TTF per Independent Response Adjudication Committee (IRAC) available at May 2013 data cut[#]

Clinical outcomes used to inform the economic model are highlighted in bold
Source: table B.5 (pages 25), company submission

FIRST
Definition of outcomes

Outcome	Definition
Progression-free survival	Time from randomisation until documented disease progression (based on International Myeloma Working Group [IMWG] criteria), or death
Overall Survival	Time from randomisation to death from any cause
Response rates	Response based on IMWG response criteria Overall confirmed myeloma response rate (ORR; ≥ PR) together with the relative proportions in each response category examined
Time to treatment failure	Time from randomisation to discontinuation of study treatment for any reason including disease progression, toxicity, start of another anti-myeloma treatment and death
Time to next treatment	Time from randomisation to the start of a non-protocol anti-myeloma treatment
PFS2*	Time from randomisation to 2nd objective progressed disease, start of 3rd line therapy or death from any cause

IMWG, International Myeloma Working Group; *PFS2 not included in economic model or decision problem
Source: table B.5 (pages 25), company submission

FIRST
Patient Characteristics

Characteristic	FIRST (n = 1,623*)	
	LEN+DEX (n = 535)	MPT (n = 547)
Median age, years (min–max)	73.0 (44.0–91.0)	73.0 (51.0–92.0)
% ≤ 75 years / >75 years[a]	65.2 / 34.8	65.6 / 34.4
Male, n (%)	294 (55.0)	287 (52.5)
% Race Asian / Black / Caucasian	7.5 / 1.7 / 88.6	8.0 / 0.9 / 89.8
% ECOG PS 0 / 1 / 2 / ≥3	29.0 / 48.0 / 22.2	28.5 / 50.3 / 20.3
% ISS staging[b] Stage I or II / Stage III	59.6 / 40.4	59.0 / 41.0
% Cytogenetic risk[c] Adverse / non-adverse risk / favourable hyperdiploidy / normal	31.8 / 55.7 / 20.9 / 27.1	34.6 / 51.6 / 18.6 / 25.8
Multiple myeloma subtype IgA / IgG / Not available[#] [#]Includes light chain disease	25.8 / 62.4 / 9.2	22.5 / 64.0 / 11.0

Source: adapted from table B.12 (page 35-37), company submission

FIRST

Key results at January 2016 data cut-off

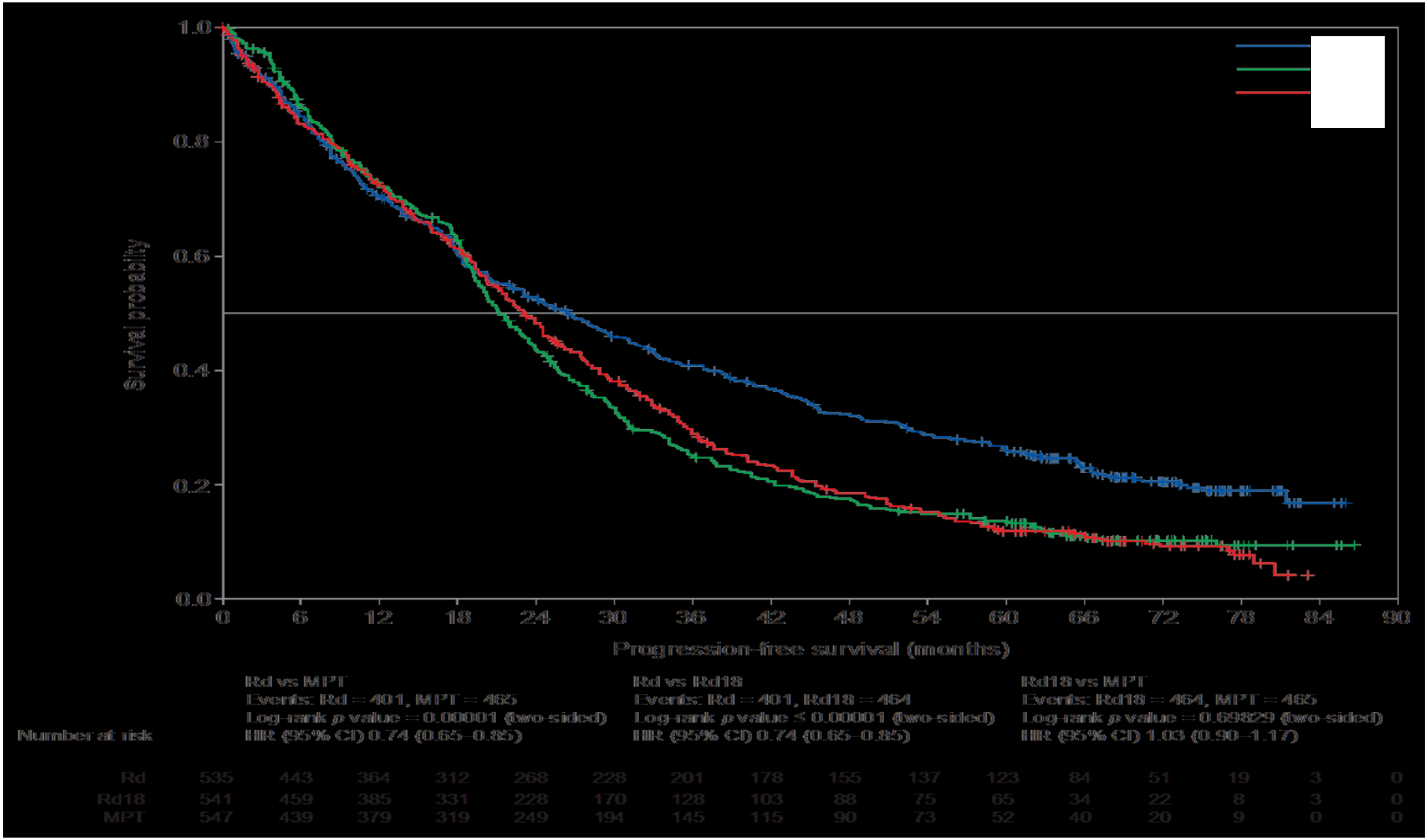
	LEN+DEX (n=535)	MPT (n=547)	Hazard ratio (95% CI)
Primary outcome			
Median PFS, months	26.5	23.0	0.74 (0.65–0.85)
Secondary outcomes			
Median OS, months	59.1	49.1	0.78 (0.62–0.92)
Median PFS2, months	42.9	35.0	0.74 (0.64–0.85)
ORR, %	80.7	67.5	OR: 2.02 (1.53–2.68)
Median TTP, months	31.3	24.4	0.64 (0.54–0.75)
Median DOR, months	31.5	22.1	0.61 (0.51–0.72)
Median months to 2nd line treatment, months	36.7	26.7	0.63 (0.54–0.73)

PFS, Progression-free survival; OS, overall survival; PFS2, Time from randomisation to 2nd PFS event; ORR, overall response rate; OR, odds ratio; TTP, time-to-progression; DOR, Duration of response

Source: adapted from table B.14 (page 45), company submission

FIRST

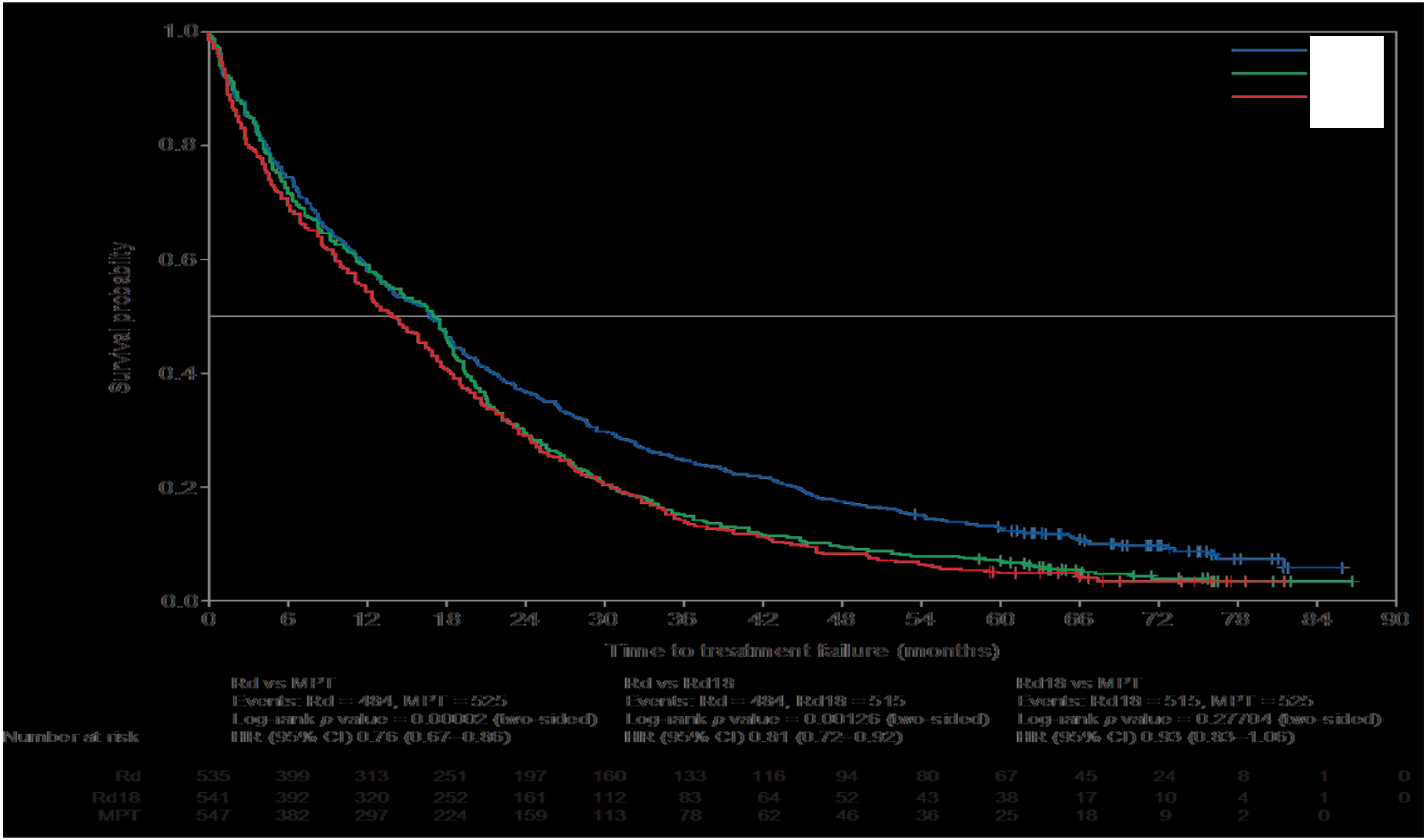
PFS, January 2016



Source: Figure B.6 (page 52), company submission

FIRST

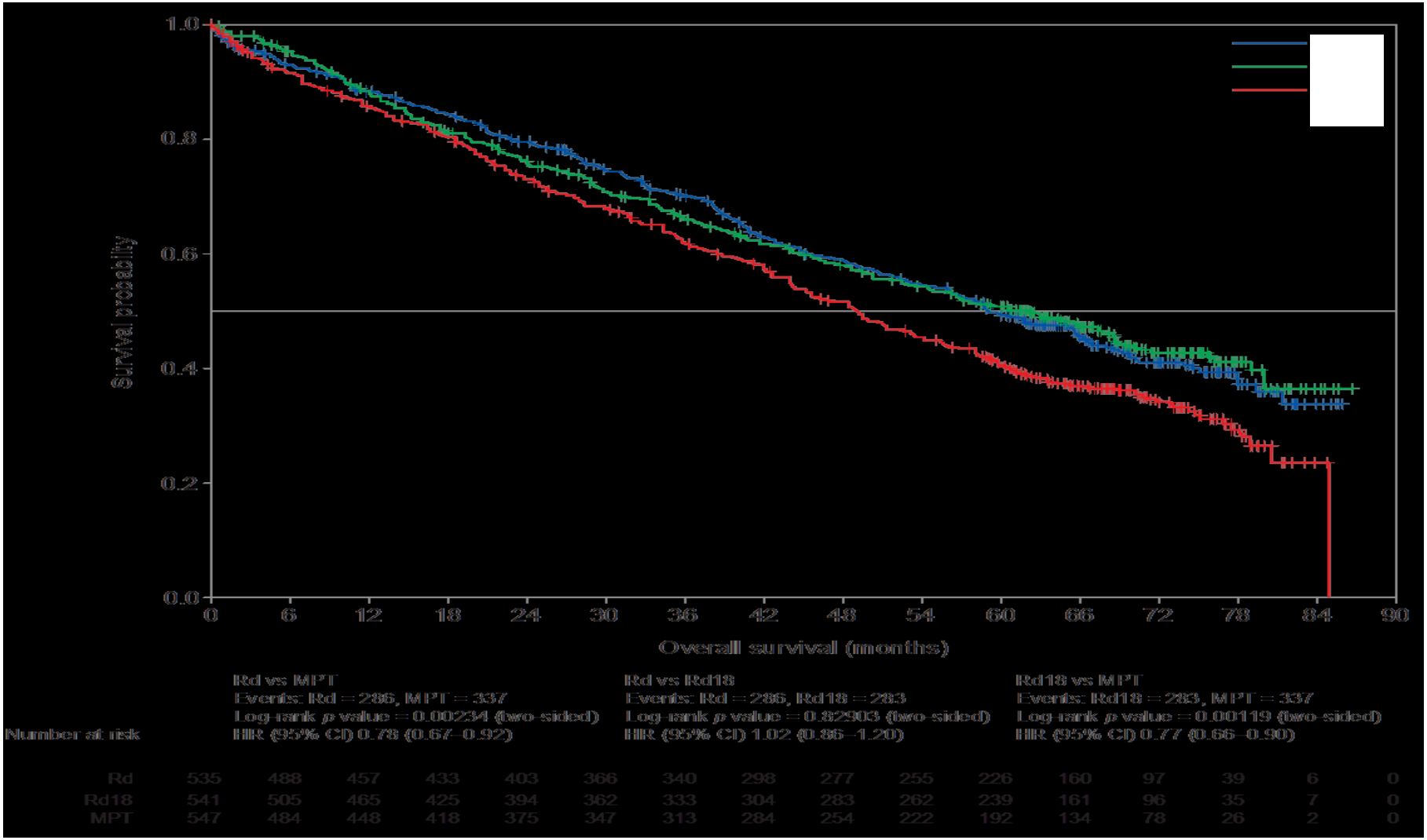
Time to treatment failure, January 2016



Source: Figure B.8 (page 56), company submission

FIRST

OS, January 2016



Source: Figure B.7 (page 53), company submission

FIRST

Subsequent anti-myeloma therapies (post hoc analysis)

	LEN+DEX (n=535) n (%)	MPT (n=547) n (%)
Patients who had any subsequent therapy[a]	299 (55.9)	381 (69.7)
type of drugs in all subsequent therapy regimens:		
Lenalidomide	75 (25.1)	264 (69.3)
Bortezomib / carfilzomib	236 (78.9)	277 (72.7)
Thalidomide	67 (22.4)	38 (10.0)
Glucocorticoid	277 (92.6)	357 (93.7)
Alkylating agents	213 (71.2)	188 (49.3)
Other therapies	93 (31.1)	99 (26.0)

[a]Based on the ITT population.
Source: Table B.16 (page 63), company submission

Indirect comparison

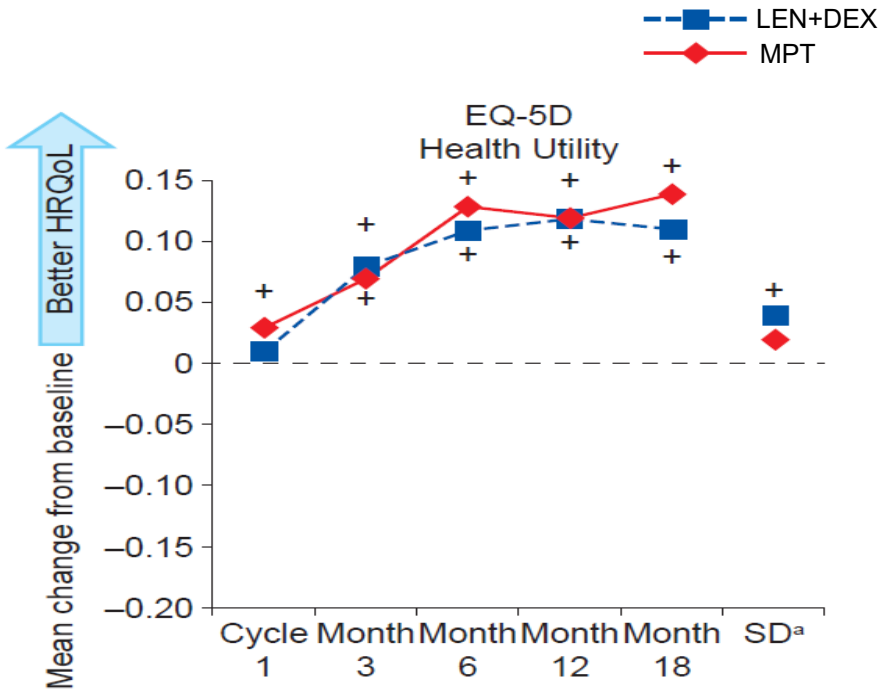
- To estimate OS and PFS the company use a fixed effects, constant hazard ratios model. Random effects and fractional polynomial models are investigated in exploratory analyses
- ERG considers:
  - There is uncertainty due to the sparseness of the network
  - Baseline characteristics were well distributed across the four trials
  - Use of fixed effects and constant hazard ratios in primary analysis appropriate

Comparison	**Progression-free survival HR (95% credible interval)**	**Overall survival HR (95% credible interval)**
LEN+DEX vs. MPT	**0.74 (0.65, 0.85)**	**0.78 (0.67, 0.91)**
LEN+DEX vs. VMP	0.74 (0.52, 1.05)	**0.70 (0.50, 0.98)**
VMP vs MPT*	1.00 (0.72, 1.38)	1.11 (0.82, 1.50)

*VMP vs MPT comparison is used to inform the economic model
Source: Adapted from table A.6 (page 13), company submission; Values in bold are statistically significant at the 0.05 significance level.

Health-related quality of life (HRQoL)
EQ-5D

- EQ-5D-3L data collected from FIRST trial used in the economic model
- No difference between LEN+DEX and LEN+DEX limited to 18 cycles, so company pooled results to compare with MPT
  - ERG assessed unpooled HRQoL and concluded pooling appropriate
- Statistically significant improvements from baseline, but no statistically significant difference between arms
- Only EORTC VMP HRQoL data from the VISTA trial (see next slide)
- VMP EQ-5D values obtained by mapping from EORTC data

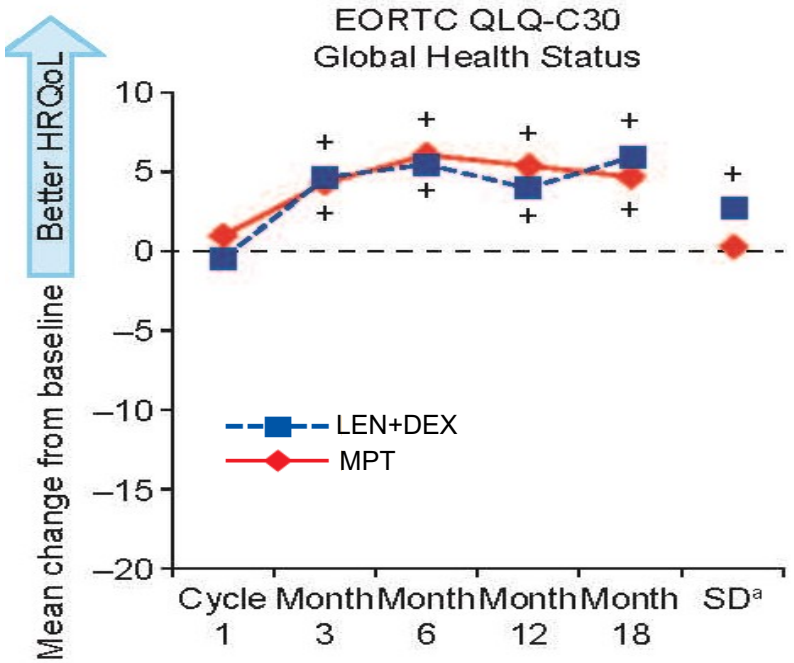


Source: Figure B.11 (page 61), company submission

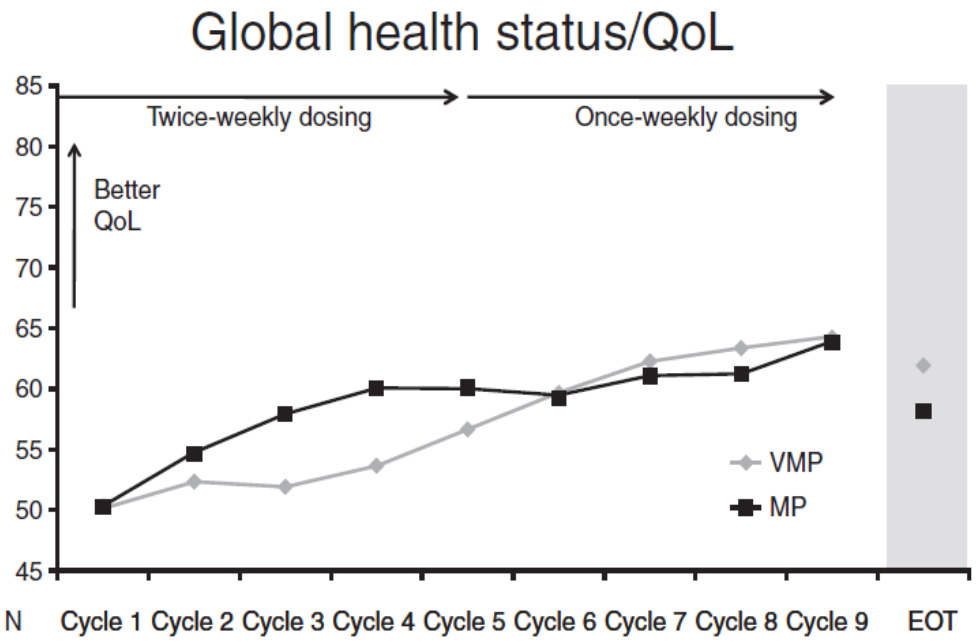
Health-related quality of life (HRQoL)
EORTC QLQ-C30

- VMP showed clinically meaningful, transitory HRQoL decrements with VMP and relatively lower HRQoL vs. MP during early treatment cycles
- No significant differences reported between treatment groups for LEN+DEX and MPT, although LEN+DEX demonstrated significantly greater reduction in disease symptoms and side effects of treatment

FIRST trial



VISTA trial



Source: Figure B.9 (page 59), company submission and Figure 1, Delforge 2012

Adverse events

- Grade 3+ adverse events with incidence over 5% used to inform economic model

		LEN+DEX (FIRST)	MPT (FIRST)	VMP (VISTA*)
Key Grade 3+ adverse event, %	Neutropenia	29.5	44.9	40
	Thrombocytopenia	9	11.1	38
	Anaemia	19	18.9	19
	Leukopenia	5	9.8	24
	Peripheral neuropathy	1.1	9.4	13
Serious adverse events, %		71.1	49.9	46
Discontinuations due to treatment related AEs, %		12	13.9	15

*Naïve comparison
Sources: Adapted from table D.63 (page 34), Company appendices

- In the FIRST trial peripheral sensory neuropathy was the only adverse event that lead to discontinuation in more than 2% of patients, at 6.7% in the MPT group

Key issues for consideration
Clinical evidence

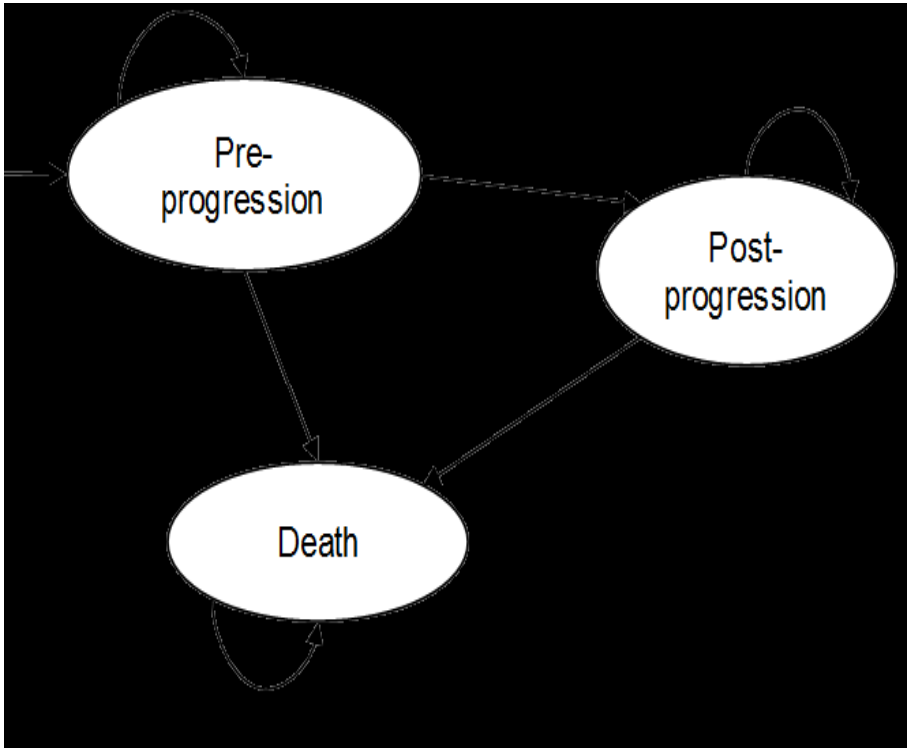
- Where will the technology be used in the treatment pathway?
- Is it acceptable to focus the value proposition on those unable to have thalidomide?
- Do the comparator regimes chosen by the company represent established NHS practice in England?
- Do the subsequent treatment therapies used in the trial company represent NHS practice in England?
- Is the clinical evidence generalisable to UK clinical practice for people who are unable to take thalidomide?
- Is the company's approach to the indirect comparison appropriate to make a comparison of LEN+DEX vs. VMP?
- Is the technology clinically effective?

Cost effectiveness evidence

Company submission section 5

Model structure

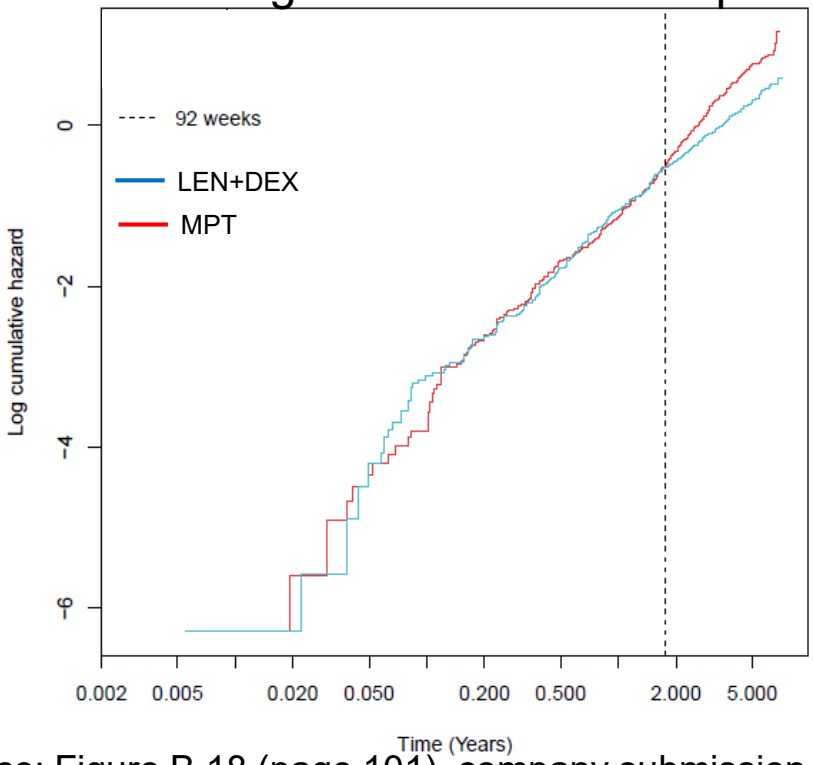
- Hybrid model structure consisting of partitioned survival analysis (for the time-period <92 weeks) and thereafter multi-state Markov model
- Time horizon: 25 years
- Starting age: 65 years
- Cycle length: 28 days with half-cycle correction
- 3.5% discounting for costs and health benefits
- UK NHS perspective



Overall and Progression-free survival
Transition probabilities

- PFS log-cumulative hazard plot show divergence at 92 weeks
- Likely due to different treatment durations – LEN+DEX continues until toxicity or progressive disease, whereas MPT a maximum of 72 weeks
- Company use OS and PFS KM data for weeks 0-92
- ≥92-weeks both OS and PFS transitions defined by constant probability transition matrices
- OS plots do not show divergence, but approach requires OS and PFS to be modelled simultaneously
- ERG considers that the company's methodological and structural choices appear to be reasonable overall

PFS Log-cumulative hazard plot



Source: Figure B.18 (page 101), company submission

Overall and Progression-free survival
Rd and MPT

- Company and ERG consider model provides a good fit to the observed Kaplan-Meier data

PFS

OS

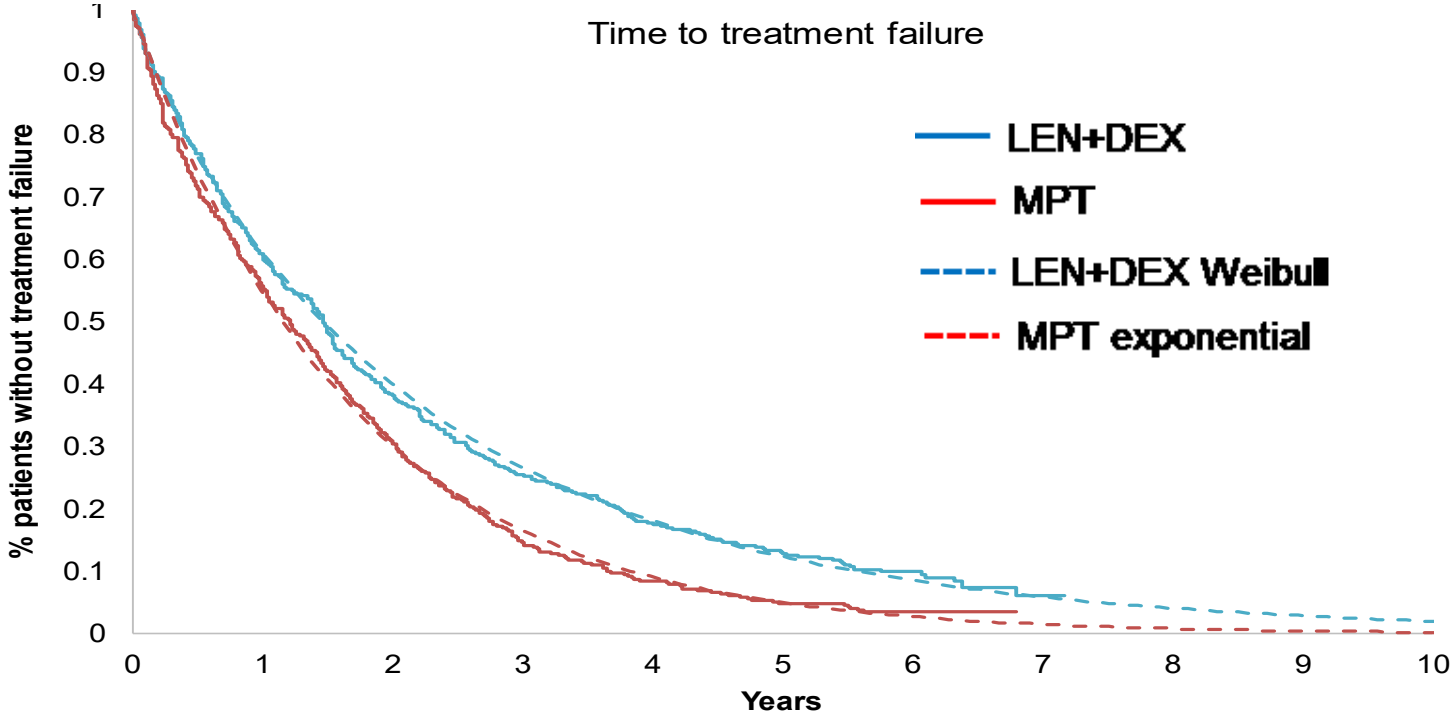
Source: figure B.19 (page 102), company submission

Overall and Progression-free survival
VMP

- HRs for VMP versus MPT from the NMA were applied to the MPT PFS and OS curves predicted by the model
- The mean HRs of VMP vs MPT were 1.00 for PFS and 1.11 for OS
- MPT chosen as reference treatment due to relative maturity of the MPT data, it also being a fixed-duration therapy and the regimen also including melphalan and prednisone.
- The ERG notes that MPT is closer than LEN+DEX to VMP in the network of trials diagram. It considers that the approach taken is appropriate.

Time to Treatment failure (TTF)
Company approach

- Company use fully-fitted parametric curves to extrapolate TTF
- Weibull for LEN+DEX arm and Exponential for MPT arm based on AIC and BIC statistics
- For VMP company assume TTF is equal to PFS up to the maximum treatment duration, as no data is available from the VISTA trial



Source: figure B.22 (page 102), company submission

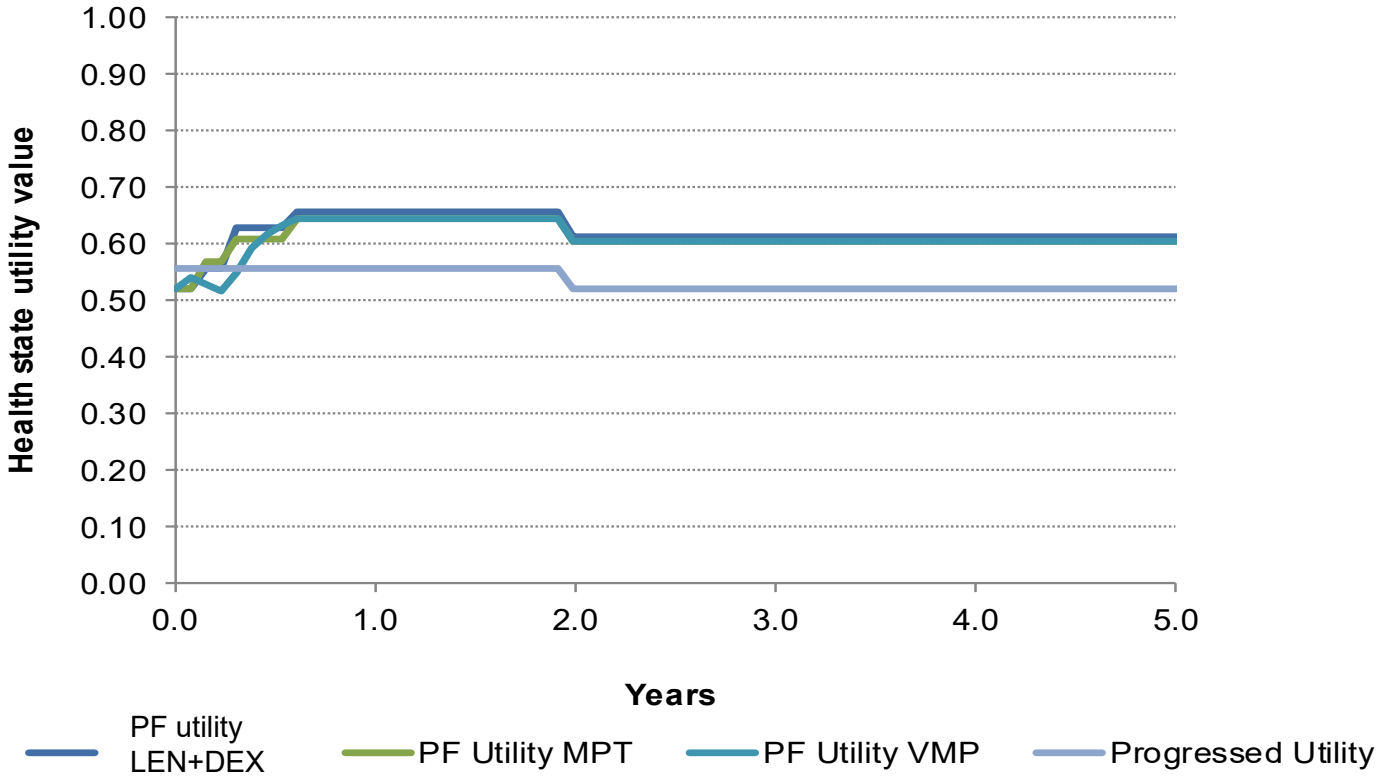
Time to Treatment failure (TTF)
ERG comments

- ERG note that TSD14 states the same parametric curve should be fitted for both treatment arms
  - Weibull distribution visually provides a better overall fit for both LEN+DEX and MPT than the exponential distribution

- ERG considers that assuming the TTF curve for VMP is equal to PFS curve is inconsistent with the approach taken for LEN+DEX and MPT
  - As PFS for MPT and VMP are similar (HR=1), ERG consider a better approach is for the TTF curve for VMP to be equal to that of MPT

Utility values
Company approach

- Progression-free: Regression model with treatment coefficient using EQ-5D data from FIRST trial provides utility for LEN+DEX and MPT. VMP calculated by mapping EORTC from VISTA trial to EQ-5D
- Post-progression: Based on FIRST EQ-5D, independent of treatment



Source: figure B.23 (page 116), company submission

Utility values
ERG comments

- ERG consider it appropriate to include a treatment coefficient (which leads to slightly higher LEN+DEX utilities) as this accounts for the expected improvement in treatment-related AEs for LEN+DEX compared with MPT
- However, no good evidence that higher utilities continue after MPT treatment stopped. ERG prefer that utilities are the same after this point
- VMP is administered in 42 day treatment cycles, whereas the utility has been assigned to 28 day cycles. ERG correct this error in their analysis
- Company does not use mapping algorithms used in TA228. However this is not expected to have a large impact on model results
- ERG considers that the utilities are uncertain because:
  - utilities for progressed disease are based only on a single outpatient visit post-progression
  - utility values used for VMP are mapped from EORTC
  - company does not state how missing HRQoL data were estimated

Resources use and costs

- Dosing data for drug costs taken directly from the FIRST trial for LEN+DEX and MPT. VMP costs estimated using proportion of eligible patients on LEN+DEX
  - Company investigated using mean relative dose intensity to estimate costs in a scenario analysis
- Company also included administration costs, concomitant medications, and costs for adverse events
  - ERG note that administration cost of VMP is based on 'Daycase and Regular Day/Night' cost code. The ERG prefer to also include Outpatient administration costs (£199 and £212 for 1st and subsequent chemotherapy administrations respectively)
- ERG had several comments on the subsequent treatment assumptions
- Otherwise, ERG concluded that the approach taken by the company for estimating health care resources and costs is reasonable

Resources use and costs
ERG comments: subsequent treatment

- ERG consider that thalidomide should not be a possible subsequent therapy to reflect the company's focus on those unable to have thalidomide
- Expert clinical advice also suggests people would not be retreated with LEN+DEX, as they had become resistant to it
- ERG note that changes to subsequent treatments to reflect clinical practice may impact overall survival, which the ERG are not able to quantify. For this reason ERG consider these changes are exploratory.

	Company base case			ERG alternative analysis		
	Bort	**Thal**	**Len**	**Bort**	**Thal**	**Len**
Treatment choice of those who receive 2nd line therapy (%)						
LEN+DEX	59.9	12.0	13.7	85.6	-	-
VMP	14.0	39.9	14.6	33.7	-	34.8
Treatment choice of those who receive 3rd line therapy (%)						
LEN+DEX	55.0	17.2	18.9	91.1	-	-
VMP	26.6	29.1	43.0	38.0	-	60.8

Bort, bortezomib-based regimes; Thal, thalidomide-based regimes; Len, lenalidomide-based regimes
Source: adapted from table 25 (page 90), table 42 (page 109) and table 44 (page 109), ERG report

Base case results

For those who are unable to have thalidomide

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Company – Deterministic					
VMP	[redacted]	[redacted]	-	-	-
LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company – Probabilistic					
VMP	[redacted]	[redacted]	-	-	-
LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

VMP, bortezomib melphalan prednisone; LEN+DEX, lenalidomide low dose dexamethasone until disease progression; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Source: table B.50 (page 141) and table B.51 (page 142), company submission

- Company considered that lenalidomide would not be cost-effective for the population who are able to have thalidomide
  - The company's deterministic ICER for this population was [redacted]

Sensitivity analyses
Probabilistic sensitivity analysis

- 1000 iterations; variation based upon distributional information
- [redacted] probability LEN+DEX is cost-effective at £30,000 per QALY

Source: figure B.24 (page 142), company submission

Sensitivity analyses
Tornado diagram

- ICER sensitive to varying the overall survival hazard ratio

Source: figure B.26 (page 143), company submission

Key scenario analyses
Equivalence between VMP and MPT

- Company and ERG note that OS HR for VMP versus MPT in the NMA has a wide credible interval (OS HR 1.11, 95% CrI: 0.82, 1.50)
- ERG note that clinical outcomes for VMP and MPT were similar in TA228
- Company state that an equivalent OS would lead to an increase in subsequent LEN+DEX use than reported in VISTA trial, and therefore prefer a scenario which also includes equivalent subsequent therapy

	Incr. Costs	Incr. QALY	ICER
Company base-case model	[redacted]	[redacted]	[redacted]
Scenario analyses			
No difference in OS between VMP and MPT	[redacted]	[redacted]	[redacted]
+ equal subsequent therapy use between VMP and MPT	[redacted]	[redacted]	[redacted]

Source: table 39 (page 107), ERG report and table B.52 (page 146), company submission

Key scenario analyses
PAS implementation

- Lenalidomide has a new complex PAS which will become operational on positive guidance from ID474 **or** the ongoing ID667 appraisal
- The new complex PAS restricts the cost of lenalidomide to [redacted] cycles, whereas the old (currently operational) PAS caps the cost to 26 cycles
- All analyses assume that any subsequent lenalidomide treatment in the comparator arm is capped at 26 cycles

	Incr. Costs	Incr. QALY	ICER	Change
Company base-case model	[redacted]	[redacted]	[redacted]	-
Scenario analyses				
New PAS (XX cycle cap) operational in comparator arm	[redacted]	[redacted]	[redacted]	[redacted]

Source: table 46 (page 111), ERG report

Key scenario analyses
Other scenario analyses

- The company conducted further scenario analyses, and noted that the ICER was not sensitive to using different assumptions

	Incr. Costs	Incr. QALY	ICER	Change
Company base-case model	[redacted]	[redacted]	[redacted]	-
Company scenario analyses				
Assume VMP duration of treatment from TA228	[redacted]	[redacted]	[redacted]	[redacted]
Use RDI for drug costs	[redacted]	[redacted]	[redacted]	[redacted]
Remove subsequent thalidomide costs	[redacted]	[redacted]	[redacted]	[redacted]
Include subsequent-treatment disutilities	[redacted]	[redacted]	[redacted]	[redacted]

Source: table B.52 (page 146), company submission

ERG preferred analysis
Changes to company's base case

- The ERG preferred the following assumptions:
  - That TTF for VMP is equal to TTF of MPT, and a Weibull distribution is used for MPT (Page 33)
  - Using the same HRQoL after MPT/VMP treatment has finished (Page 35)
  - Cycle length correction for VMP utilities (page 35)
  - Alternative VMP administration costs (page 36)
- Additional alternative analysis where patients do not receive thalidomide or retreatment with LEN+DEX as a 2nd line or 3rd line treatment (page 37)

	Incr. costs	Incr. QALYs	ICER	Change
Company base case	[redacted]	[redacted]	[redacted]	-
ERG preferred analysis	[redacted]	[redacted]	[redacted]	[redacted]
ERG alternative analysis	[redacted]	[redacted]	[redacted]	[redacted]

Source: Adapted from table 48 (page 112) and table 50 (page 114), ERG report

ERG preferred analysis

Impact of individual changes

	Incr. Costs	Incr. QALY	ICER	Change
Company base-case model	[redacted]	[redacted]	[redacted]	-
ERG preferred assumptions				
TTF changes	[redacted]	[redacted]	[redacted]	[redacted]
Cycle length correction	[redacted]	[redacted]	[redacted]	[redacted]
Equal HRQoL after treatment	[redacted]	[redacted]	[redacted]	[redacted]
VMP administration costs	[redacted]	[redacted]	[redacted]	[redacted]
No 2nd / 3rd line thalidomide	[redacted]	[redacted]	[redacted]	[redacted]
No 2nd / 3rd line thalidomide and no retreatment with LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]

Source: table 59 (page 139), ERG report

ERG Comments
Conclusions

- Model structure is appropriate and consistent with the clinical disease pathway. The approach provided a good fit against the observed trial data from MM-020.
- The company has appropriately tested a range of their key model assumptions. Alternative scenarios provided broadly similar results to the base case.
- HRQoL used follows NICE reference case. However, some uncertainty around values for progressed disease and values taken by mapping from EORTC
- Health care resources and costs are reasonable. There is some uncertainty around the costing of subsequent treatment costs.
- Although the clinical trials used in the model did not specifically recruit patients who are unable to take thalidomide, expert clinical advice to the ERG is that this would not influence the generalisability of the clinical effectiveness outcomes
- The ERG's preferred base case analysis increases the ICER from the company's base case analysis, but it remains below £30,000 per QALY.

Innovation

- Company consider that lenalidomide represents a step-change in the management of transplant-ineligible NDMM, as:
  - Compared with thalidomide and bortezomib, it has a different mechanism of action and toxicity profile, which allows for continuous use to suppress residual disease and extend the period of first remission.
  - As an oral therapy, lenalidomide provides an alternative to IV and injectable therapies such as bortezomib, which have to be given in the hospital setting.
  - It may be given in a two-drug combination that does not include melphalan, which may be more tolerable to older frail patients.

End-of-life criteria

- The company do not consider lenalidomide meets the criteria for end-of-life
  - The median survival in the comparator arm is 49.1 months
- The ERG agree with the company conclusion

Equality

Issue identified at scoping stage:

- People with multiple myeloma attend specialist treatment units for injectable treatment. These patients are often less mobile or live a long distance from their treatment centre meaning they are less likely to receive these treatments

Preliminary view as to what extent these potential equality issues need addressing by the Committee

- The benefits of different mode of administration will be taken into account in the appraisal.

Key issues for consideration
Cost-effectiveness evidence

- Is the model structure appropriate for decision-making?
- What is the committee's opinion on the ERG's change to:
  - TTF, so that VMP is equal to MPT, and a Weibull distribution is used
  - Using the same HRQoL after MPT/VMP treatment has finished
  - Cycle length correction for VMP utilities
  - Alternative VMP administration costs
- What is the most plausible effectiveness of VMP relative to MPT ? Equivalence or superiority of MPT (reducing the risk of death by 10%)?
- Should the following subsequent treatments be included in the model:
  - Thalidomide?
  - Retreatment with lenalidomide and dexamethasone?
  - Newer treatments (POM+DEX and PANO+PORT+DEX)?
- Are there any innovation and equality considerations?
- What is the most plausible ICER?

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lenalidomide for previously untreated multiple myeloma [ID474]

Document B

Company evidence submission

October 2017

File name	Version	Contains confidential information	Date
ID474 Lenalidomide Document B SUBMITTED 230419 [redacted]	4	Yes	23 April 2019

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Abbreviations

AE	adverse event
AIC	Akaike information criterion
AMT	anti-myeloma therapy
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplant
ASH	American Society of Hematology
BCSH	British Committee for Standards in Haematology
BIC	Bayesian information criterion
BNF	British National Formulary
BOR	bortezomib
CEAC	cost-effectiveness acceptability curves
CI	confidence interval
CODA	convergence diagnosis and output analysis
CSR	clinical study report
CTD	cyclophosphamide, thalidomide and dexamethasone
CTDa	attenuated cyclophosphamide, thalidomide and dexamethasone
CR	complete response
CrCl	creatinine clearance
CrI	credible interval
DEX	dexamethasone
DOR	duration of response
DSMC	Data Safety Monitoring Committee
EBMT	European Group for Blood and Marrow Transplantation
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EHA	European Haematology Association
EMA	European Medicines Agency
eMIT	electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC Quality of Life Questionnaire – Core 30
EORTC QLQ-MY20	EORTC Quality of Life Questionnaire – Multiple Myeloma 20
EPAR	European Public Assessment Report
EQ-5D	5-dimension European Quality of Life questionnaire
ERG	evidence review group
ESA	erythropoietin stimulating agents
ESMO	European Society for Medical Oncology

FDA	Food and Drugs Administration
G-CSF	granulocyte-colony stimulating factor
HMRN	Haematological Malignancy Research Network
HR	hazard ratio
HRG	healthcare resource group
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IFM	*Intergroupe Francophone du Myelome*
IMiD®	immunomodulatory drug
IMWG	International Myeloma Working Group
IRAC	Independent Response Adjudication Committee
ITT	intent-to-treat
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISS	International Staging System
IV	intravenous
1L	first line
2L	second line
3L	third line
LDH	lactate dehydrogenase
LLoT	last line of treatment
LY	life-year
MDS	myelodysplastic syndrome
MID	minimal important difference
MIMS	monthly index of medical specialities
MM	multiple myeloma
MP	melphalan and prednisone
MPR	melphalan, prednisone and lenalidomide
MPR-R	melphalan, prednisone and lenalidomide followed by lenalidomide maintenance
MPT	melphalan, prednisone and thalidomide
MRC	Medical Research Council
MSM	multi-state Markov
MTA	multiple technology appraisal
MTC	mixed treatment comparison
NCCN	National Comprehensive Cancer Network
NDMM	newly diagnosed multiple myeloma
NICE	National Institute for Health and Care Excellence
NK	natural killer
NMA	network meta-analysis
NR	not reported

OLEP	open-label extension phase
ORR	overall response rate
OS	overall survival
OWSA	one-way sensitivity analysis
PANO	panobinostat
PAS	patient access scheme
PD	progressive disease
PFLY	progression-free life-year
PFS	progression-free survival
PFS2	progression-free survival 2
PO	*per os* (orally)
PP	post-progression
PPS	post-progression survival
PPLY	post-progression life-year
PPP	pregnancy prevention programme
PR	partial response
PrePS	pre-progression
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QoL	quality of life
RBC	red blood cell
RCT	randomised controlled trial
Rd	lenalidomide and low-dose dexamethasone until disease progression
RD	lenalidomide and high-dose dexamethasone
RDI	relative dose intensity
Rd18	18 cycles of lenalidomide and low-dose dexamethasone
RRMM	relapsed/refractory multiple myeloma
SACT	Systemic Anti-Cancer Therapy
SAE	serious adverse event
SC	subcutaneous
SD	stable disease
SE	standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLR	systematic literature review
SmPC	summary of product characteristics
SoC	standard of care
SPM	second primary malignancy
STA	single technology appraisal
TEAE	treatment-emergent adverse event

TSD	technical support document
TTF	time to treatment failure
TTP	time to progression
TTR	time to response
VAT	value added tax
VGPR	very good partial response
VMP	bortezomib, melphalan and prednisone
VTE	venous thromboembolism
WCBP	women of childbearing potential
WTP	willingness-to-pay

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The objective of this single technology appraisal (STA) is to appraise the clinical and cost effectiveness of lenalidomide according to its license variation allowing its use in transplant-ineligible newly diagnosed multiple myeloma (NDMM) patients. This license variation was granted by the European Medicines Agency (EMA) in February 2015.[1,2]

The final scope was issued in August 2017 as detailed in Table 1.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with previously untreated MM for whom stem-cell transplantation is considered inappropriate.	Adults with previously untreated MM for whom stem-cell transplantation is considered inappropriate.	
Intervention	Lenalidomide in combination with dexamethasone	Lenalidomide in combination with dexamethasone	
Comparator (s)	• Thalidomide in combination with an alkylating agent and a corticosteroid For people who are unable to tolerate, or have contraindications to thalidomide: • Bortezomib in combination with an alkylating agent and a corticosteroid	• Thalidomide in combination with an alkylating agent and a corticosteroid For people who are unable to tolerate, or have contraindications to thalidomide: • Bortezomib in combination with an alkylating agent and a corticosteroid	CTD was not considered a relevant thalidomide-based combination as it is unlicensed. MPT was considered a suitable proxy for CTD as it was deemed by clinical specialists who took part in TA228[3] to be equivalent in terms of efficacy and toxicity, and is also similar in terms of cost.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • time to next treatment • time to treatment failure • adverse effects of treatment	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • time to next treatment • time to treatment failure • adverse effects of treatment	

	• health-related quality of life.	• health-related quality of life.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.	The reference case has been adhered to (Section B.3.2). A Patient Access Scheme (PAS) for lenalidomide has already been approved by the Department of Health for this indication. This is an extension of the Treatment continuation scheme (TCS™) which is already in operation for TA322 in myelodysplastic syndromes (MDS) with deletion 5q and for TA171 in multiple myeloma, and has been in operation in the NHS since 2009. The PAS is a complex, finance-based scheme; the cost of lenalidomide is capped at 26 cycles, after which point Celgene bears the cost and the drug is free to the NHS. For this appraisal, Celgene propose to modify the PAS so that lenalidomide is given free of charge after [redacted] cycles for all indications, conditional on a positive recommendation.	
Subgroups to be considered	People who are unable to tolerate, or have contraindications to thalidomide (per comparators section of final scope)	A cost-effectiveness analysis has been conducted in the subgroup of people who are unable to tolerate, or have contraindications to thalidomide.	
Special considerations including issues	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does	N/A	N/A

related to equity or equality	not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.		

Key: MM, multiple myeloma; **N/A**, not applicable; **NHS**, National Health Service; **NICE**, National Institute for Health and Care Excellence

B.1.2 Description of the technology being appraised

The summary of product characteristics (SmPC) and European public assessment report (EPAR) can be found in Appendix C.

Table 2 Technology being appraised

UK approved name and brand name	Lenalidomide (REVLIMID®▼)
Mechanism of action	Lenalidomide is an oral, immunomodulatory drug (IMiD®), derived from thalidomide.[4] Lenalidomide acts intracellularly by binding cereblon, a component of an ubiquitin ligase enzyme complex. In the presence of lenalidomide, cereblon binds the lymphoid transcriptional factors Aiolos and Ikaros, which leads to their ubiquitination and subsequent degradation, thus resulting in cytotoxic and immunomodulatory effects.[5,6]
Marketing authorisation/CE mark status	Lenalidomide was granted a EMA marketing authorisation on 19 February 2015 for the indication in this submission: use in patients with NDMM who are not eligible for transplantation.[1,2]

Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	***Indications***
	Lenalidomide as combination therapy is indicated for the treatment of adult patients with previously untreated MM who are not eligible for transplantation.[5] Other existing indications include:
	• MM
	  ○ Lenalidomide as monotherapy is indicated for the maintenance treatment of adult patients with NDMM who have undergone autologous stem cell transplantation.[5]
	  ○ Lenalidomide in combination with dexamethasone is indicated for the treatment of MM in adult patients who have received at least one prior therapy.[5]
	• Myelodysplastic syndromes
	  ○ Lenalidomide is indicated for the treatment of adult 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.[5]
	• Mantle cell lymphoma
	  ○ Lenalidomide is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma.[5]
	Restrictions
	• Lenalidomide is contraindicated by known hypersensitivity

	to the active substance or to any of the excipients and in women who are pregnant and women of childbearing potential unless all of the conditions of the PPP are met.[5] • Lenalidomide treatment must not be started if the absolute neutrophil count is less than 1.0 × 10^9/L and/or platelet counts are less than 50 × 10^9/L. • Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors. • The SmPC provides more detail and describes other warnings and precautions not described here.[5]
Method of administration and dosage	Oral treatment. Lenalidomide dosage is 25 mg/day in a 21/28 day cycle.
Additional tests or investigations	• Owing to its structural similarities with thalidomide, lenalidomide is contraindicated in WCBP, and male partners of WCBP, unless appropriate contraceptive measures and pregnancy testing are carried out. WCBP should have two 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.[5]
List price and average cost of a course of treatment	***List cost per 21-tablet pack***[7] 25 mg, £4,368; 20 mg, £4,168; 15 mg, £3,969; 10 mg, £3,780; 7.5 mg, £3,675; 5 mg, £3,570; 2.5 mg, £3,426. ***Average cost of a course of treatment*** The cost-effectiveness analysis predicts the following cost per course of lenalidomide in combination with dexamethasone: [redacted] [redacted]
Patient access scheme (if applicable)	Subject to approval by the Department of Health, the cost of lenalidomide is capped at [redacted] cycles, after which point Celgene bears the cost and the drug is free to the NHS (Table 1).

Key: EMA, European Medicines Agency; **MM**, multiple myeloma; **NDMM**, newly diagnosed multiple myeloma; **NHS**, National Health Service; **PPP**, pregnancy prevention programme; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **SmPC**, Summary of Product Characteristics; **WCBP**, women of child-bearing potential.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Overview of the disease

Multiple myeloma (MM) is a rare, incurable, malignant haematological disease arising from the monoclonal expansion of plasma cells in the bone marrow.[8,9] It represents approximately 1% of all incident cancers globally and results in more than 43,000 deaths annually worldwide.[10] MM is primarily a disease of the elderly, and the median age at diagnosis ranges, by study, from 69 to 73 years.[11,12] At diagnosis, more than two-thirds of patients are aged ≥ 65 years[12] and nearly half are aged ≥ 75 years.[13]

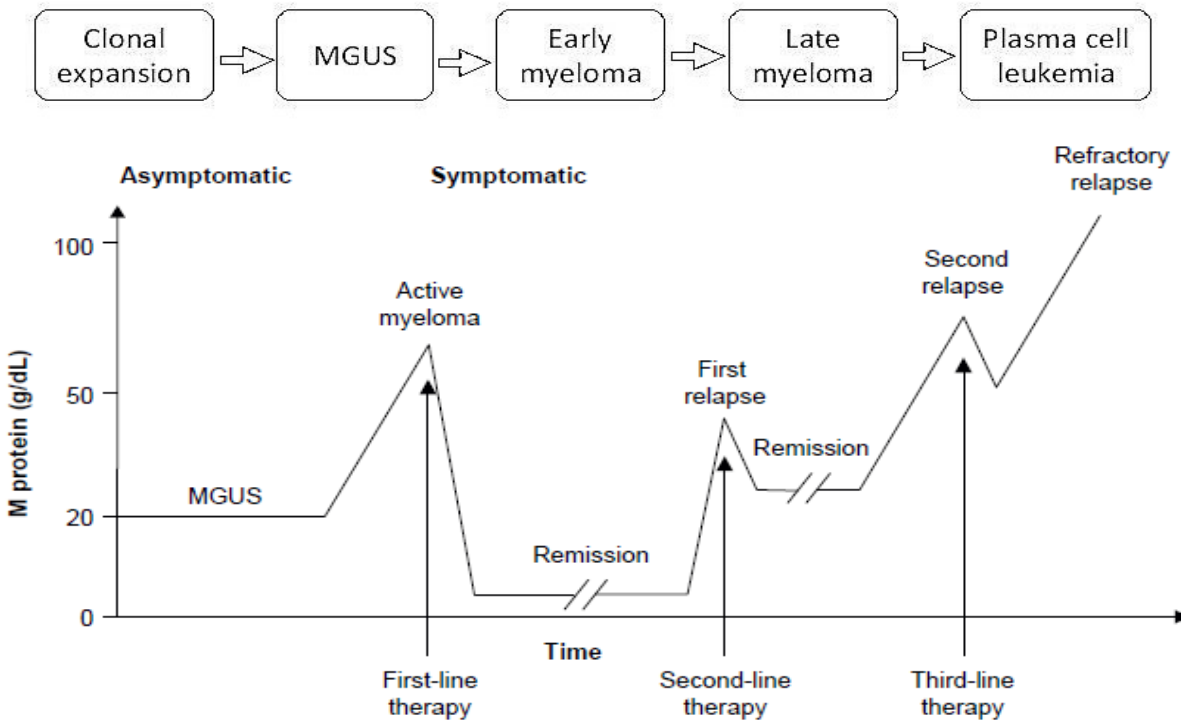
Patients suffer from a range of debilitating symptoms, including skeletal destruction, which arises from activation of osteoclasts by MM cells and leads to lytic bone lesions (80% of patients), pathological fractures (26%), bone pain (58%), mobility problems, osteoporosis (23%), impaired bone marrow function, hypercalcaemia (symptomatic or asymptomatic; 10–30% of patients), anaemia (75% of patients) and general ill health.[14-17] Secretion of M-proteins by plasma cells results in renal insufficiency (up to 50%) and kidney failure, and patients are more susceptible to recurrent infections because of a compromised B-cell lineage.[16-18] The course of disease is not uniform and varies according to factors related to:

- the patient (age, frailty and renal function)[17,19]
- tumour load, assessed by the International Staging System (ISS) as well as Durie and Salmon stages of classification[20,21]
- cytogenetic anomalies, including translocations (4;14) and (14;16) and deletion 17p[22,23] (these high-risk cytogenetic anomalies were incorporated into a revised ISS staging system in 2015)[24]
- sensitivity of the tumour to treatment.[25]

While treatment can result in remission, the course of the disease in response to current treatment regimens is characterised by cycles of remission and relapse.[26] Many patients relapse because of the continued presence of resistant cells in the bone marrow in the form of minimal residual disease[27] which is an independent predictor of progression-free survival (PFS) and overall survival (OS), or they will

discontinue therapy due to toxicity, for example peripheral neuropathy.[17,28] With increasing lines of therapy, there is a decreasing duration of response (DOR) and ultimately development of refractory disease.[17,26,29] Figure 1 shows the typical pattern of MM patient remission and relapse in response to treatment.

Figure 1 Characteristic pattern of remission and relapse following conventional chemotherapy in multiple myeloma



Key: MGUS, monoclonal gammopathy of undetermined significance.
Source: Borello 2012.[26]

This pattern of regression and remission and the presence of minimal residual disease suggest that continuous therapy is required to suppress residual disease, maximise depth of response and prolong the first remission, a key factor in patient survival.[26,27,30] This is particularly important for older transplant-ineligible patients who may not respond to rescue therapy at the time of first relapse or have the opportunity to receive multiple lines of treatment.[31,32] Furthermore, the period of first remission is likely to be when patients enjoy the best quality of life (QoL) over the duration of the disease.[29,33] This is echoed in National Institute for Health and Care Excellence (NICE) guidance TA228, where the committee stated that "The main objective of first-line therapy is to achieve a period of stable disease (termed the plateau phase) for as long as possible, thereby prolonging survival and maximising quality of life".[3]

Historically, melphalan and prednisone (MP) formed the mainstay of front-line therapy in transplant-ineligible patients with NDMM, producing responses in approximately 50% of patients with a median OS of 3 years.[34-36] Treatment with MP has largely been superseded by fixed treatment durations of oral thalidomide with an alkylating agent and steroid (melphalan, prednisone and thalidomide [MPT] or cyclophosphamide, thalidomide, and dexamethasone [CTD]) or intravenous (IV) or subcutaneous (SC) bortezomib (bortezomib, melphalan, and prednisone [VMP]) combinations, all which can delay relapse compared with MP.[17,37-39] Both MPT and VMP have shown OS advantage over MP, but this has not been demonstrated for CTD.[37,38,40] Continuous treatment with these approved regimens are limited not only by their respective licences but also by their toxicity.[41,42,37,39]

The toxicity profile of thalidomide is associated with a number of adverse events such as constipation, peripheral sensory neuropathy, neutropenia, thrombocytopenia and nausea. In addition, paraesthesia, dizziness, peripheral neuropathy, leukopenia and lymphopenia are also reported with thalidomide combinations.[5,42,43] In particular, peripheral neuropathy is a very common and potentially severe adverse reaction to treatment with thalidomide that may result in irreversible damage. Thalidomide may also potentially aggravate existing neuropathy, which can sometimes occur as part of the background myeloma disease. In this instance, the thalidomide SmPC recommends that it should not be used in patients with clinical signs or symptoms of peripheral neuropathy.[42] In the UK-based Medical Research Council Myeloma IX study, continued use of thalidomide as a maintenance therapy after 6–9 cycles of induction with CTD was associated with poor tolerability, with discontinuation rates due to adverse events (AEs) reaching 50%, making it unsuitable for long-term therapy.[37]

B.1.3.2 Impact of the disease and current treatments on patients and their carers

Multiple myeloma has a significant emotional impact on patients, particularly when they relapse on their initial front-line treatment. In one study, patients reported feeling scared, depressed, worried, confused, frustrated and powerless. Some patients also reported that multiple relapses were associated with loss of hope as they felt they were “getting closer to the end”.[44]

As the disease progresses, patients not only face a worse prognosis but also a greater symptomatic burden including the cumulative effects of treatment.[25,44,45] It is therefore important, particularly in older transplant-ineligible patients to delay relapse and maximise the benefit of front-line treatment while preserving QoL. Treatment with VMP has been show to impact QoL compared to MP.[46] Similarly, patients receiving MPT have been shown to have more disease symptoms and side effects of treatment relative to the lenalidomide based treatment (see section B.2.6.11).[47]

In addition to the symptomatic, health-related quality of life (HRQoL) and anxiety burden of the disease itself, current treatments also add to the patient burden. Treatment options, including bortezomib, require IV or SC administration in a hospital setting and are associated with at least four hospital visits per month.[41] Such a requirement for frequent hospital visits is a particular issue for patients with MM who are often frail, elderly and have mobility problems related to their condition.[19,48]

The disease and its treatment also impacts employment. One study showed that only half of patients who underwent intensive MM treatment were still employed after diagnosis, with a mean age of 61 years.[49]

Caregivers are also affected; treatment for MM often involves, weeks or months away from home, requiring a large time commitment from caregivers as well as patients themselves.[49] Caregivers can suffer financial difficulties as a result of a relative being diagnosed with MM; they may suffer from loss of wages, difficulty in paying bills, lack of sick leave and premature use of retirement funds.[50]

B.1.3.3 Clinical pathway of care and context of the proposed use of the technology

Table 3 shows the current clinical pathway of care in England and the proposed placement of lenalidomide and low-dose dexamethasone given until disease progression (Rd) within the pathway. Rd will not displace thalidomide as a first-line treatment option for transplant-ineligible patients with NDMM, rather it is envisaged that Rd is likely to partially displace first-line bortezomib combinations and lead to a reduction in the use of lenalidomide in subsequent lines of therapy. Use of bortezomib with an alkylating agent and steroid has been recommended as first-line

treatment by NICE only for patients who are unable to tolerate or who have contraindications to thalidomide.[3,51]

Lenalidomide has an improved safety profile compared with thalidomide which means that patients who are unable to tolerate or who have contraindications to thalidomide may also benefit from Rd in addition to bortezomib combinations.[5,31,42,43] Patients who receive thalidomide are more likely to suffer from AEs such as constipation, peripheral sensory neuropathy (up to 20% of patients with MM present with peripheral neuropathy at diagnosis[28]), neutropenia, thrombocytopenia, nausea, paraesthesia and dizziness.[43] In practice, patients who present with predisposing conditions that make them more susceptible to these AEs may benefit from receiving Rd. Providing physicians with the ability to prescribe Rd will allow a wider choice of therapeutic options and treatment to be tailored to patients' individual needs.

Within this submission, a cost-effectiveness analysis comparing Rd with VMP shows efficacy advantages of Rd. In addition, Rd offers both advantages in term of toxicity, QoL and administration compared to bortezomib combinations.

Table 3 Current clinical pathway of care for patients with multiple myeloma in England

Therapy line	Guidance	Transplant eligible patients with MM	Transplant ineligible patients with MM
1st Line	NICE TA311[52] NICE TA228[3]	• BOR + DEX or BOR + THAL + DEX induction followed by ASCT[52]	• THAL+ alkylating agent + corticosteroid (e.g. MPT)[3] • If THAL intolerant /contraindicated BOR + MP[3] ○ **Proposed use of Rd**
2nd Line	NICE TA129[53] NICE TA457[54]	• BOR ± DEX having received 1 prior therapy[53] • CAR + DEX having received 1 prior therapy which did not include BOR • LEN + DEX (subject to ongoing NICE appraisal) • Conventional chemotherapy (including cyclophosphamide and melphalan) ± steroid[a] • A minority of patients may receive a second ASCT	
3rd Line onwards	NICE TA171[55] NICE TA380[56]	• LEN + DEX[55] • PANO + BOR + DEX[b] [56]	
4th Line onwards	NICE TA427[57] CDF 2017[58]	• POM + LoDEX[57] • Daratumumab monotherapy (subject to ongoing NICE appraisal) • BEN combinations[d] (via CDF) where all other treatments contraindicated or inappropriate [58] • Conventional chemotherapy (inc. cyclophosphamide and melphalan) ± steroid ± THAL re-treatment[c]	

[a] Primarily received by patients who cannot tolerate THAL, have received BOR at first-line and have recently initiated 2nd line treatment as BOR retreatment is no longer funded by the CDF therefore availability is limited.
[b] PANO+BOR+DEX is reimbursed in patients who have received ≥ 2 prior lines of treatment including BOR + IMiD;
[c] THAL retreatment can only be used in patients who are THAL eligible (i.e., not those who are THAL intolerant or contraindicated);
[d] BEN is usually used at 4th line onwards (via the CDF).
Key: ASCT, autologous stem cell transplant; **BEN**, bendamustine; **BOR**, bortezomib; **CAR, carfilzomib; CDF**, National Cancer Drugs Fund; **DEX**, dexamethasone; **IMiD**, immunomodulatory drug ; **LEN**, lenalidomide; **LoDEX**, low dose dexamethasone; **MM**, multiple myeloma ; **MP**, melphalan, prednisone; **MPT**, melphalan, prednisone, thalidomide; **NICE**, National Institute for Health & Care Excellence; **PANO**, panobinostat; **POM**, pomalidomide; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **THAL**, thalidomide.
Sources: NICE TA311, 2014[52]; NICE TA228, 2011;[3] NICE TA129, 2007;[53] NICE TA457, 2017 ;[54] 2009;[55] NICE TA380;[56] NICE TA427;[57] NHS CDF List, 2017.[58]

B.1.3.4 Supporting Clinical Guidelines Relevant to this Submission

A number of clinical practice guidelines have been published on the treatment of NDMM.[17,18,59-61] Some, like the British Committee for Standards in Haematology (BCSH),[17] pre-date the licensing of lenalidomide for transplant-ineligible patients; however some of the more up to date guidelines refer to the use of Rd based on MM-020 study results.[60,61]

European guidelines

The European Society for Medical Oncology (ESMO) has recently (2017) published MM specific clinical practice guidelines dealing with treatment of patients with transplant-ineligible NDMM.[60] These guidelines recommend either VMP or Rd (based on data from MM-020,[31] the pivotal trial in this submission) as a first option for symptomatic transplant-ineligible NDMM patients outside of clinical trials.

National Comprehensive Cancer Network guidelines (United States)

The National Comprehensive Cancer Network (NCCN) recommends Rd as a Category 1 option (i.e. based on high-level evidence, with uniform NCCN consensus that the intervention is appropriate) for treatment of patients with NDMM who are ineligible for transplantation.[61] The NCCN scores Rd as 4 out of 5 for efficacy, safety, quality of evidence and consistency of evidence, which is higher than or equivalent to the scores for comparative agents (Table 4).[61]

Table 4 Summaries of NCCN evidence blocks for Rd vs relevant comparators

	Rd	VMP	MPT
Efficacy	4	4	4
Safety	4	3	3
Quality of evidence	4	4	4
Consistency of evidence	4	4	4

(5 = best, and 1 = worst)
Key: MPT, melphalan, prednisone and thalidomide; **NCCN**, National Comprehensive Cancer Network; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **VMP**, bortezomib, melphalan, and prednisone.
Source: NCCN, 2016.[61]

B.1.4 Equality considerations

No equality issues relating to the use of lenalidomide have been identified or are anticipated.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

Appendix D provides full details of the systematic literature review (SLR) used to identify and select clinical evidence relevant to this submission. Of the 23 studies identified by the SLR (eligibility criteria are detailed in Table 56), only 4 studies were considered relevant to the decision problem specified in the final scope (Table 1); 1 study containing lenalidomide (MM-020[31,43]) and 3 studies containing evidence for comparators used to form the network meta-analysis described in Section B.2.9.

B.2.2 List of relevant clinical effectiveness evidence

Details of MM-020 are given in Table 5 including primary and secondary outcomes and which of these were used in the economic model.

Table 5 Clinical effectiveness evidence

Study	MM-020 (FIRST),[43] Benboubker *et al.* 2014[31]				
Study design	Phase 3, multicentre, multinational, randomised, open-label, three-arm study to compare efficacy and safety of two lenalidomide regimens for two different treatment durations with MPT of a fixed treatment duration.				
Population	Patients with NDMM aged 65 years or over ineligible for stem cell transplantation, or aged under 65 and not a candidate for stem cell transplantation.				
Intervention(s)	Rd				
Comparator(s)	MPT (Rd18)[a]				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	X
	No			No	
Rationale for use in the model	MM-020 was identified by the SLR and is considered relevant to the decision problem.				
Reported outcomes specified in the decision problem	*Primary outcome* • PFS (Used in the economic model[b]) *Secondary outcomes* • OS (Used in the economic model) • Response rates • TTF (Used in the economic model) • Time to next treatment (second-line AMT) • Adverse Events (Used in the economic model) • HRQoL, using QLQ-C30, QLQ-MY20, EQ-5D. (EQ-5D-3L used in the economic model)				
All other reported outcomes	• TTR • TTP • DOR • PFS2				

[a] The primary comparison was Rd vs MPT. Rd18 is not of relevance to the decision problem for this appraisal.
[b]21Jan 2016 data cut, investigator assessment using EMA censoring rules.
Key: AMT, anti-myeloma therapy; **DOR**, duration of response; **EMA**, European Medicines Agency; **EQ-5D**, 5-dimension European Quality of Life questionnaire; **HRQoL**, health-related quality of life; **MM**, multiple myeloma; **MPT**, melphalan, prednisone and thalidomide; **NDMM**, newly diagnosed multiple myeloma; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **PFS2**, time from initial randomisation to second objective PD, start of third-line therapy or death from any cause, whichever comes first; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, 18 cycles of lenalidomide and low-dose dexamethasone; **SLR**, systematic literature review ; **TTF**, time to treatment failure; **TTP**, time to progression; **TTR**, time to response.
Source: Clinical Study Report CC-5013-MM-020/IFM 07-01.[43]

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

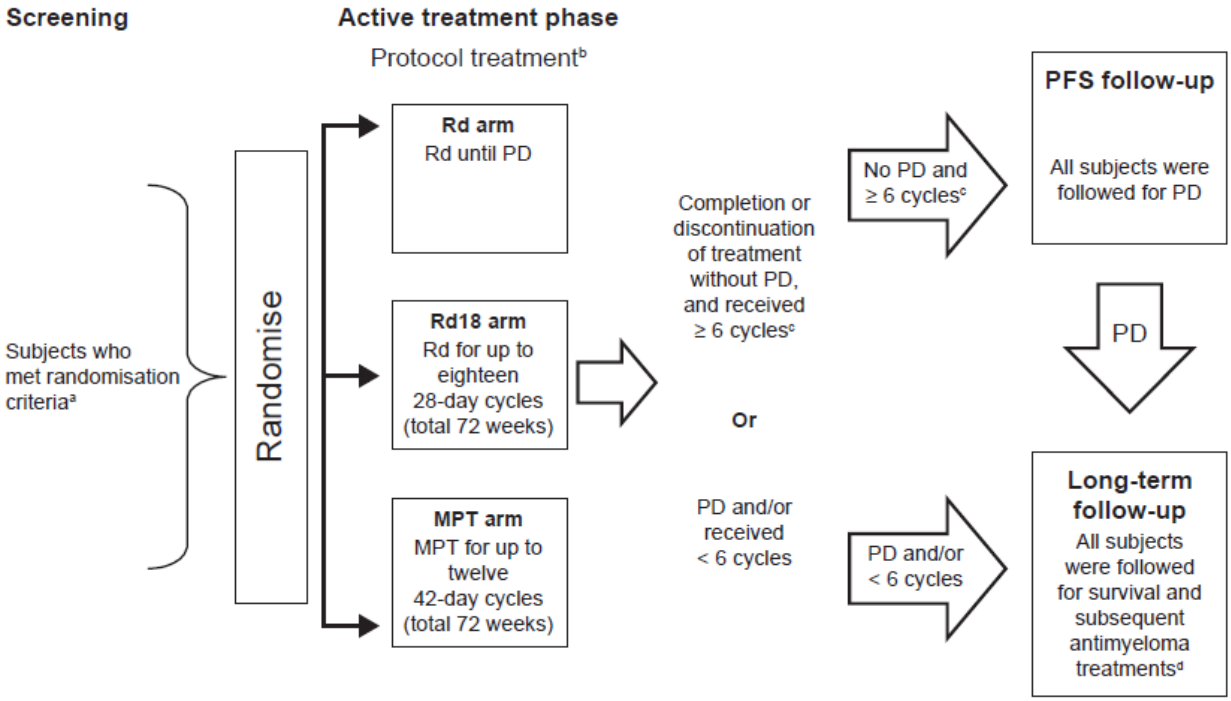
The MM-020 study[31,43] is the primary source of data for this submission and the methodology is described below. All data in this submission are taken from the MM-

020 clinical study report (CSR, CC-5013-MM-020/IFM 07-01),[43] unless otherwise stated/referenced.

B.2.3.1 Study design

The MM-020 study (NCT00689936) was a randomised, multicentre, open-label, pivotal, phase 3 trial in transplant-ineligible patients with NDMM (n = 1623). The three treatment arms comprised Rd (i.e. lenalidomide and low-dose dexamethasone given until disease progression) or lenalidomide and low-dose dexamethasone for 18 cycles over 72 weeks (Rd18), or a recognised standard of care, MPT administered for 72 weeks.[31,43] The study design of MM-020 is summarised in Figure 2.

Figure 2 MM-020 study design



[a] Patients were stratified at randomisation as described in Table 11.
[b] The initial dose of melphalan and thalidomide was adjusted according to age. Patients > 75 years received a reduced starting dose of dexamethasone (20 mg), melphalan (0.20 mg/kg), and thalidomide (100 mg).
[c] Patients in the Rd18 arm who completed 18 cycles, patients in the MPT arm who completed 12 cycles, and patients in any arm who discontinued owing to reasons other than PD, such as unacceptable toxicity, entered the PFS follow-up phase as long as they received at least 6 cycles of study treatment and their treating physician determined that additional new anti-myeloma therapy was not required before the development of PD.
[d] Patients who discontinued early from active treatment (< 6 cycles) were followed for PD in the long-term follow-up phase with the same frequency of assessment.
Key: MPT, melphalan, prednisone and thalidomide; **PD**, progressive disease; **PFS**, progression-free survival; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 18 cycles.
Source: Clinical Study Report CC-5013-MM-020/IFM 07-01.[43]

B.2.3.2 MM-020 eligibility criteria

The key inclusion and exclusion criteria for patients entering the MM-020 study are presented in Table 6.

Table 6 Patient eligibility criteria for MM-020

Inclusion criteria	Exclusion criteria
• Newly diagnosed symptomatic MM (all three criteria required): Monoclonal plasma cells in the bone marrow ≥ 10% and/or presence of a biopsy-proven plasmacytoma Monoclonal protein present in the serum and/or urine Myeloma-related organ dysfunction AND measurable disease by protein electrophoresis analyses in serum and/or urine • Age ≥ 18 years • If younger than 65 years of age, was not a candidate for SCT because the patient declined SCT or SCT was not available • An ECOG performance status score of 0, 1 or 2 • Compliance with pregnancy prevention measures • Able to adhere to study visit schedule and other protocol requirements	• Prior anti-myeloma treatment (except for radiotherapy and treatment with bisphosphonates or a single short course of glucocorticoids) • Non-secretory MM by SPEP and UPEP analyses • An ECOG performance status score > 2 • Any serious medical condition placing a patient at unacceptable risk, such as unstable cardiac disease (e.g. NYHA heart failure class III–IV) • Pregnancy or lactating women • ANC < 1000/μL, a platelet count (without transfusion) < 50,000 cells/μL • A serum aspartate aminotransferase or alanine aminotransferase level > 3.0 × ULN • Renal failure requiring haemodialysis or peritoneal dialysis • Prior history of malignancies, other than MM unless free of the disease for ≥ 3 years[a] • Unwilling to undergo antithrombotic prophylaxis • PN ≥ grade 2 severity • Known HIV infection or active hepatitis (A, B or C) • Primary amyloidosis and myeloma complicated by amyloidosis

[a]Exceptions include: basal cell and squamous cell carcinoma of the skin, carcinoma *in situ* of the cervix and breast, incidental histological finding of prostate cancer.
Key: ANC, absolute neutrophil count; **ECOG**, Eastern Cooperative Oncology Group; **HIV**, human immunodeficiency virus; **NYHA**, New York Heart Association; **MM**, multiple myeloma; **PN**, peripheral neuropathy; **SCT**, stem cell transplant; **SPEP**, serum protein electrophoresis; **ULN**, upper limit of normal; **UPEP**, urinary protein electrophoresis.
Source: Clinical Study Report CC-5013-MM-020/IFM 07-01.[43]

B.2.3.3 MM-020 study site locations and setting

The International Phase III MM-020 study was co-sponsored by Intergroupe Francophone du Myelome (IFM) and Celgene Corporation (Summit, New Jersey,

USA). The study enrolled 1,623 patients from 246 sites across 18 countries in Europe (165 sites), North America (39 sites), and the Asia-Pacific region (42 sites).[43] Of the patients randomised, 72 patients were recruited from 16 centres in the UK, making results also applicable to UK practice.[43] Please refer to clinicaltrials.gov (NCT00689936) for a full list of sites.

B.2.3.4 MM-020 study drugs and concomitant medications

The protocol treatments of the three arms of MM-020 (Figure 2) are illustrated in Table 7.

Table 7 MM-020 study drug, dose and duration

Study Arm	Study drug dosing	Treatment duration
Rd	• 25 mg lenalidomide on days 1 to 21 of a 28-day cycle. • 40 mg dexamethasone on days 1, 8, 15 and 22 of a 28-day cycle.	Until disease progression or unacceptable toxicity.
Rd18	• 25 mg lenalidomide on days 1 to 21 of a 28-day cycle. • 40 mg dexamethasone on days 1, 8, 15 and 22 of a 28-day cycle.	18 cycles (72 weeks)
MPT	• 0.25 mg/kg melphalan, on days 1 to 4 of a 42-day cycle. • 2 mg/kg prednisone: on days 1 to 4 of a 42-day cycle. • 200 mg thalidomide on days 1 to 42 of a 42-day cycle.	Maximum of twelve 42-day cycles (72 weeks)

MPT, melphalan, prednisone and thalidomide**; Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 18 cycles.

Dose adjustments were made dependant on age, renal function, and neutrophil and platelet count (Table 8). Dose delays and reductions were permitted in case of study treatment toxicity.

Table 8 MM-020 dose adjustments based on patient age and renal function

Drug (study days / cycle duration)	Adjustment	≤ 75 years	> 75 years
Lenalidomide (1–21/28 days)	CrCl: < 30 mL/min CrCl: 30–50 mL/min CrCl: > 50 mL/min	15 mg QOD 10 mg 25 mg	15 mg QOD 10 mg 25 mg
Dexamethasone (1, 8, 15, 22/28 days)	N/A	40 mg	20 mg
Melphalan (1–4/42 days)	N/A	0.25 mg	0.20 mg
	CrCl: < 50ml/min ANC < 1.5X10^9/L Platelet count: < 100 x 10^9/L	0.125 mg/kg	0.10 mg/kg
Prednisone (1–4/42 days)	N/A	2 mg/kg	2 mg/kg
Thalidomide (1–42/42 days)	N/A	200 mg	100 mg

Key: **ANC**, absolute neutrophil count; **CrCl**, creatinine clearance; **N/A**, not applicable; **QOD**, every other day.
Source: Clinical Study Report CC-5013-MM-020/IFM 07-01 (section 9.4).[43]

Bisphosphonates and other supportive therapies including antithrombotic, anti-infective, erythropoietin-stimulation agents and granulocyte-colony stimulating factor (G-CSF) were allowed at the investigator's discretion. Table 9 summarises the use of these concomitant therapies by patients during the MM-020 study.[43]

Table 9 Use of concomitant therapy during the active treatment phase in the safety population

Category	Rd N = 532
Antithrombotic, n (%)	531 (99.8)
Heparin, n (%)	48 (9.0)
Warfarin, n (%)	32 (6.0)
Anti-infective, n (%)	430 (80.8)
Erythropoietin stimulating agent, n (%)	160 (30.0)
Granulocyte-colony stimulating factor, n (%)	93 (17.5)

Key: Rd, lenalidomide and low-dose dexamethasone until disease progression.
Source: Clinical Study Report CC-5013-MM-020/IFM 07-01.[43]

Concomitant use of other anti-myeloma therapy (AMT) while the subject was on study drug was prohibited. The protocol also required a 14-day washout period from previous steroid therapy before the patient entered the study.

B.2.3.5 Outcome measures

There have been a number of analyses in the course of study MM-020. Current status is that the final planned PFS and OS data are available. Table 10 highlights outcomes measures specified in the scope, relevant outcome data available and the associated data used in the economic model.

The main data presented in this submission are:

- 24 May 2013: pre-planned data cut-off date for final PFS analysis based on assessments by an Independent Response Adjudication Committee (IRAC) using International Myeloma Working Group (IMWG) response criteria[62] with a median follow-up of 37 months. At this time sufficient events had occurred to trigger final analysis of PFS. A planned interim analysis of OS was conducted at this time point.[31,43]
- 21 January 2016: pre-planned data cut-off for final OS, with a median follow-up of 67 months. At this time point *post-hoc* updated analysis of PFS, progression-free survival 2 (PFS2), time to progression (TTP), time to treatment failure (TTF), duration of response (DOR), time to response (TTR), time to second AMT and overall response rate (ORR) by investigator were conducted, with a median follow up of 67 months.[43]

Throughout this submission, data are presented primarily for the most up-to-date data cut from 21 January 2016.[43]

Table 10 Outcome measures for MM-020 and relevance to economic model.

Endpoint type	Key efficacy measures[a]	Description	Data available		Data used in economic model
			24 May 2013 data cut[c]	21 Jan 2016 data cut[d]	
Primary endpoint	PFS[b]	PFS was defined as time from randomisation until documented disease progression, or death, whichever occurred earlier. PFS was assessed by the IRAC based on IMWG response criteria.[62] • A secondary PFS analysis was carried out by investigator assessment based on IMWG response criteria. • A sensitivity analysis was also performed comparing FDA censoring rules[63] (used in both IRAC and investigator assessments) and EMA censoring rules.[64]	✓ (Investigator assessment, FDA censoring) (IRAC assessment FDA and EMA censoring)	✓ (Investigator assessment, FDA and EMA censoring)	21 Jan 2016 data cut, Investigator assessment, EMA censoring
Secondary outcomes	OS	Time from randomisation to death from any cause.	✓	✓	21 Jan 2016 data cut.
	Response rate	The primary response analysis was based on the assessments by the IRAC using IMWG response criteria.[62] Response was also assessed by investigator using IMWG criteria. The overall confirmed myeloma response rate (ORR; ≥ PR) together with the relative proportions in each response category were examined for IRAC and investigator assessments.	✓ (Investigator and IRAC assessments)	✓ (Investigator assessment)	×
	TTF	Time from randomisation to discontinuation of study treatment for any reason including disease progression, toxicity, start of another anti-myeloma	✓ (IRAC assessment)	✓ (Investigator assessment)	21 Jan 2016 data cut (Investigator assessment).

		treatment and death.			
	Time to second-line AMT	Time from randomisation to the start of a non-protocol AMT.	✓ (Investigator assessment)	✓ (Investigator assessment)	×
Other outcomes	HRQoL	QLQ-C30, QLQ-MY20, EQ-5D.	✓	×	21 Jan 2016 data cut (EQ-5D-3L)
Safety	Safety	Evaluation of adverse events, physical examination (including vital signs/neurological examination), clinical laboratory evaluations (including haematology), electrocardiogram, concomitant medications/therapies, a pregnancy testing and pregnancy prevention risk management plan and incidence of SPM.	✓	✓	21 Jan 2016 data cut

[a]Study MM-020 also reported the secondary outcome DOR, TTR and the exploratory outcomes TTP and PFS2. However, as none of these outcomes are part of the final scope (Table 1), and are not used by the economic model, they have not been included here.
[b]The primary comparison was Rd vs MPT.
[c]24 May 2013 data was from a pre-planned data cut with final analysis of PFS.
[d]21 January 2016 data was from a pre-planned data cut with final analysis of OS.

Key: AMT, anti-myeloma therapy; **DOR**, duration of response; **EMA,** European Medicines Agency; **EQ-5D**, 5-dimension European Quality of Life questionnaire; **FDA**, Food and Drug Administration; **HRQoL**, health-related quality of life; **IMWG**, International Myeloma Working Group; **IRAC**, Independent Response Adjudication Committee; **MPT**, melphalan, prednisone and thalidomide; **ORR**, overall response rate; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **PFS2**, time from initial randomisation to second objective PD, start of third-line therapy or death from any cause, whichever comes first; **PR**, partial response; **QLQ-C30**, Quality of Life Questionnaire – Core 30; **QLQ-MY20**, Quality of Life Questionnaire – Multiple Myeloma 20; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **SPM**, second primary malignancy; **TTF**, time to treatment failure; **TTP**, time to progression; **TTR**, time to response.
Source: Clinical Study Report CC-5013-MM-020/IFM 07-01[43] and Delforge *et al.* 2015.[47]

B.2.3.6 Summary of MM-020 methodology

MM-020 methodology is summarised in Table 11.

Table 11 Summary of MM-020 methodology

Study details	MM-020
Location	246 centres treatment centres in 18 countries.
Design	Phase 3, multicentre, multinational, randomised, open-label, three-arm study to compare efficacy and safety of two lenalidomide regimens for two different treatment durations with MPT of a fixed treatment duration.
Duration of core study	Rd or Rd18 or MPT treatment phase. Follow-up until progression/relapse or survival in all three arms.
Method of randomisation	1:1:1 randomisation using a validated interactive voice-response system (IVRS) Designated research personnel were assigned unique access code envelopes, which authorised them to call the IVRS to randomise patients into the study. The IVRS presented a menu of questions, to identify the patient, confirm eligibility and enter stratification information. Following confirmation that the patient could be randomised, the IVRS assigned a randomisation identification number to the patient. The patient was issued a study drug kit corresponding to the randomised treatment group. Confirmation was sent to the study site and to Celgene.
Blinding	Open-label with assessor blinding. The study team was blinded to the data until after the database lock following the targeted number of events for the final analysis of PFS (the primary endpoint) being met. PD was confirmed by the IRAC who were blinded to treatment allocation.
Patient stratification	Age (≤ 75 years vs > 75 years) ISS disease stage (I or II vs III) Country/region
Protocol treatment	Rd: 25 mg lenalidomide on days 1 to 21 and 40 mg dexamethasone on days 1, 8, 15 and 22 of a 28-day cycle, both until disease progression or unacceptable toxicity Rd18: 25 mg lenalidomide on days 1 to 21, and 40 mg dexamethasone on days 1, 8, 15 and 22 of a 28-day cycle for a total of 18 cycles (72 weeks) MPT: melphalan: 0.25 mg/kg, days 1 to 4; prednisone: 2 mg/kg on days 1 to 4; 200 mg thalidomide on days 1 to 42 for a maximum of twelve 42-day cycles (72 weeks) Dose adjustments were made dependant on age, renal function, and neutrophil and platelet count. Dose delays and reductions were permitted in case of study treatment toxicity. All patients received protocol-specified antithrombotic prophylaxis.

	Bisphosphonates and other supportive therapies were allowed at the investigator's discretion. No cross-over between treatment groups was allowed.
Efficacy assessment	Response was assessed according to the International Myeloma Working Group criteria,[62] at the start of each treatment cycle and every 28 days during the follow-up phase.
Primary endpoint (including scoring methods and timings of assessments)	The primary endpoint was PFS (per FDA censoring rules). Response was assessed at 28-day intervals during both treatment (to PD development or cycle end) and follow-up phases. PFS was censored at the date when the response assessment determined lack of progression for those patients who discontinued the active treatment phase or the PFS follow-up phase before documentation of PD. If a patient initiated a new AMT regimen, then PFS was censored at the date of the last progression-free response assessment before the start date of the new regimen.
Other endpoints	OS, ORR (CR, VGPR and PR), TTR, DOR, TTF, time to second-line AMT, HRQoL, TTP and PFS2
Primary and secondary comparisons	For all efficacy endpoints, the primary comparison was between Rd and MPT, and the secondary comparisons were between Rd and Rd18, Rd18 and MPT, and Rd + Rd18 and MPT.
Subgroup analyses	Age group (≤ 75 years, > 75 years), baseline ISS (stages I or II, stage III), country: North America and Pacific Region (USA, Canada, Australia and New Zealand), Europe (Austria, Belgium, France, Germany, Greece, Italy, Portugal, Spain, Sweden, Switzerland and UK), and Asia (China, Taiwan and Republic of Korea), sex and race. Other clinical features identified as possible prognostic factors for response in patients with MM could be used as an exploratory analysis; PFS, OS and ORR could be compared between treatment arms based on the EE population using the same analysis for the ITT analyses. Exploratory analyses were conducted for PFS and OS to assess the demographic and prognostic factors that most affected treatment outcome and to adjust the treatment comparisons for these variables. The variables to be evaluated included age, sex, baseline ISS score, baseline ECOG performance status, and other relevant baseline characteristics, such as cytogenetic abnormalities. Subsequently, corresponding subgroup analyses could be performed for PFS and OS. Logistic regression could be used in an exploratory manner for time-to-event variables to assess the effects of risk factors on response rates. Summaries of demographic and baseline disease characteristics, duration of treatment, follow-up time for surviving subjects, and analyses of PFS, PFS2, and OS were generated for subjects with CR or VGPR to further our understanding of PFS, PFS2, and OS in this subgroup of subjects.
Duration of	Median of 37.0 (range 0 to 56.7) months at the time of primary endpoint

follow-up for reported analysis	assessment (24 May 2013 data cut-off) For OS, there was one interim analysis: 24 May 2013 and a final planned analysis at 21 January 2016 data-cut (67.0 months follow-up).

Key: AMT, anti-myeloma therapy; **CR**, complete response; **DOR**, duration of response; **ECOG**, Eastern Cooperative Oncology Group; **EE**, efficacy evaluable; **HRQoL**, health-related quality of life; **IRAC**, Independent Response Adjudication Committee; **ISS**, International Staging System**; ITT**, intent-to-treat; **IVRS**, interactive voice recognition system; **MM**, multiple myeloma; **MPT**, melphalan, prednisone and thalidomide; **ORR**, overall response rate; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **PFS2**, time from initial randomisation to second objective PD, start of third-line therapy or death from any cause, whichever comes first; **PR**, partial response; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 18 cycles; **TTF**, time to treatment failure; **TTP**, time to progression; **TTR**, time to response; **VGPR**, very good partial response.
Source: Clinical Study Report CC-5013-MM-020/IFM 07-01.[43]

B.2.3.7 MM-020 patient characteristics

Baseline characteristics of the study population in all treatment groups were well balanced (Table 12). The median age was 73.0 years in each of the treatment arms. The study population included 92 patients (5.7%) who were aged less than 65 years, these patients were equally distributed between treatment arms with no clinically meaningful differences in demographic or disease characteristics; however, the reasons for their transplant-ineligibility were not systematically captured. The ITT population was balanced by sex (52.6% male), and the majority were white or Caucasian (89.0%) and from Europe (68.6%). Generally, study patients had advanced disease. Of the total study population of which 35% were older than 75 years, 40.6% had ISS stage III, 9.1% had severe renal insufficiency (creatinine clearance [CrCl] < 30 mL/min), 71.2% had a history of bone disease, and 13.5% had received radiation for MM prior to treatment in the study. About a third (33.5%) of the study patients had a cytogenetic profile associated with adverse risk (t[4;14], t[14;16], del[13q] or monosomy 13, del[17p], or 1q gain).

Table 12 Baseline characteristics of patients in MM-020

Characteristic	MM-020 (n = 1,623)		
	Rd (n = 535)	Rd18 (n = 541)	MPT (n = 547)
Median age (min–max), years	73.0 (44.0–91.0)	73.0 (40.0–89.0)	73.0 (51.0–92.0)
Age distribution,[a] n (%)			
≤ 75 years	349 (65.2)	348 (64.3)	359 (65.6)
> 75 years	186 (34.8)	193 (35.7)	188 (34.4)
Male, n (%)	294 (55.0)	273 (50.5)	287 (52.5)
Race, n (%)			
Asian	40 (7.5)	43 (7.9)	44 (8.0)

Black/African–American	9 (1.7)	6 (1.1)	5 (0.9)
Hawaiian/Pacific Islander	1 (0.2)	0 (0.0)	1 (0.2)
White/Caucasian	474 (88.6)	480 (88.7)	491 (89.8)
Other	6 (1.1)	11 (2.0)	3 (0.5)
Undisclosed	5 (0.9)	1 (0.2)	3 (0.5)
ECOG performance status, n (%)			
0	155 (29.0)	163 (30.1)	156 (28.5)
1	257 (48.0)	263 (48.6)	275 (50.3)
2	119 (22.2)	113 (20.9)	111 (20.3)
≥ 3	2 (0.4)	2 (0.4)	2 (0.4)
Missing	2 (0.4)	0 (0.0)	3 (0.5)
ISS staging,[b] n (%)			
Stage I or II	319 (59.6)	322 (59.5)	323 (59.0)
Stage III	216 (40.4)	219 (40.5)	224 (41.0)
Beta-2-microglobulin, n (%)			
> 5.5 mg/L	224 (41.9)	224 (41.4)	234 (42.8)
≤ 5.5 mg/L	309 (57.8)	316 (58.4)	312 (57.0)
Missing	2 (0.4)	1 (0.2)	1 (0.2)
Creatinine clearance, n (%)			
< 30 mL/min	45 (8.4)	47 (8.7)	55 (10.1)
≥ 30–50 mL/min	126 (23.6)	120 (22.2)	126 (23.0)
≥ 50–80 mL/min	241 (45.0)	252 (46.6)	222 (40.6)
≥ 80 mL/min	123 (23.0)	122 (22.6)	144 (26.3)
Cytogenetic risk,[c] n(%)			
Adverse risk	170 (31.8)	185 (34.2)	189 (34.6)
Non-adverse risk	298 (55.7)	290 (53.6)	283 (51.6)
Favourable hyperdiploidy	112 (20.9)	103 (19.0)	102 (18.6)
Normal	148 (27.7)	131 (24.2)	141 (25.8)
Uncertain risk	38 (7.1)	56 (10.4)	39 (7.1)
Non-evaluable	34 (6.4)	35 (6.5)	45 (8.2)
Missing	33 (6.2)	31 (5.7)	31 (5.7)
MM subtype			
IgA	138 (25.8)	142 (26.2)	123 (22.5)
IgA and IgG	7 (1.3)	6 (1.1)	8 (1.5)
IgA and IgM	0 (0.0)	0 (0.0)	1 (0.2)
IgD	4 (0.7)	7 (1.3)	4 (0.7)
IgG	334 (62.4)	331 (61.2)	350 (64.0)
IgM	3 (0.6)	1 (0.2)	1 (0.2)
Not available (includes light	49 (9.2)	54 (10.0)	60 (11.0)

chain disease)			

[a] Patients were stratified at randomisation by age (≤ 75 years vs > 75 years).
[b] Patients were stratified at randomisation by stage (stage I or II vs stage III).
[c] Cytogenetic risk categories are mutually exclusive.
Definitions: adverse risk categories: t(4;14), t(14;16), del(13q) or monosomy 13, del(17p), 1q gain; **non-adverse risk categories:** favourable hyperdiploidy (t[11;14], gains of 5/9/15, normal, a normal result, gains other than 5/9/15, IgH deletion, and uncertain risk. Probes used for analysis cannot place patient in any of the other risk categories. Not evaluable: no specimen received, test failure or insufficient number of cells available for analysis.
Key: ECOG, Eastern Cooperative Oncology Group; **Ig**, immunoglobulin; **ISS**, International Staging System; **MM**, multiple myeloma; **MPT**, melphalan, prednisone and thalidomide; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 18 cycles.
Source: Clinical Study Report CC-5013-MM-020/IFM 07-01.[43]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 MM-020 sample size

The primary analysis of study MM-020 was to compare PFS in patients treated with Rd and those treated with MPT for 72 weeks. A total of approximately 1,590 patients (530 in each arm) were enrolled, with accrual of about 67 patients per month for 24 months. With a 24-month accrual period and 36-month follow-up after the study closed to accrual, a sample size of 530 patients in each treatment arm would have 80% power to detect a hazard rate ratio of 1.25 using a 2-sided log-rank test with an overall significance level of 0.05. This calculation was based on the following assumptions: an improvement in median PFS of 25% being clinically relevant; an exponential overall PFS distribution with a constant failure rate; uniform accrual during the accrual period and an approximate 10% annual drop-out rate with an exponential distribution.

Taking into account the third treatment arm (Rd18) as part of a secondary analysis to compare efficacy between Rd, Rd18 & MPT, the information required for a log-rank test to have 80% power was expected to be achieved when approximately 950 patients, across all treatment arms, had disease progression or had died.

The comparison of final OS was planned for when all patients had been followed for 5 years or had died or been lost from follow-up before 5 years. Median survival was estimated to be 56 months in the Rd treatment arm and 45 months in the MPT treatment arm and was assumed to have an exponential distribution. With 530 patients in each treatment arm, a total of 597 deaths were expected in the two

arms within 5 years (896 deaths across all three treatment arms). Based on survival curves reflective of a 25% improvement in median OS and 597 deaths, a two-sided log-rank test with a significance level of 0.05 would have a power of 78%.

B.2.4.2 MM-020 populations

The intent-to-treat (ITT) population was defined as all patients who were randomised, independent of whether they received study treatment. All patients in the ITT population were analysed according to the treatment they were randomised to receive and not according to what they actually received, if different.

The efficacy-evaluable population was defined as ITT patients who met protocol requirements (either met eligibility criteria and/or had measurable disease at baseline) and were evaluated after receiving at least one dose of study treatment. The safety population was defined as all randomised patients who received at least one dose of the study treatment. Drug exposure and all safety analyses (including AEs, deaths, serious adverse events [SAEs] and laboratory test results) were based on the safety population. Patients were analysed according to the initial treatment received.

B.2.4.3 MM-020 statistical analysis

A hierarchical, group sequential-testing procedure with appropriate alpha-spending functions, multiple-arm comparison and multiplicity-adjustment was used to control the family-wise type-I error rate in the interim and final analyses of endpoints. For PFS, the stopping boundaries for the interim analysis were based on an α-spending function of the O'Brien-Fleming type with an overall one-sided α = 0.025.[65] The two OS comparisons (Rd vs MPT and Rd18 vs MPT) were adjusted with Bonferroni procedure, in which a group sequential test with a one-sided type-I error probability of α/2 (0.0125) was run separately for each comparison. The stopping boundaries for the OS interim analyses were based on an α-spending function of the Pocock type with an overall one-sided α = 0.0125 for each of the two OS comparisons.[65,66] The other secondary endpoints were summarised at the interim analysis. No formal stopping rules were employed for these endpoints.

Details of the statistical analyses undertaken in MM-020 are described in Table 13. All efficacy endpoint analyses were based on the ITT population.

Table 13 Summary of statistical analyses used in MM-020

Outcome	Calculated as	Statistical analysis
PFS	• Time between randomisation and documented disease progression (assessed by the IRAC based on IMWG response criteria),[62] or death, whichever comes first. • Patients who withdrew for any reason or received another AMT without documented PD were censored on the date of their last adequate response assessment before receiving another AMT. Patients who were still active without PD (as determined by the IRAC) at the time of the data cut-off date were censored on the date of their last adequate response assessment.[63] • Final analysis used FDA censoring rules,[63] see Appendix C for details. • Sensitivity analysis of final analysis used EMA censoring rules,[67] see Appendix C for details.	• The KM method was used to estimate survival distribution functions for each treatment arm. The median PFS along with the 2-sided 95% CI for the median was estimated. • PFS was compared between treatment arms using an unstratified log-rank test with a two-sided significance level of 0.05. This 5% was spread over the pre-planned interim analysis and the final analysis by an O'Brien-Fleming alpha spending function.[65] • A log-rank test stratified by the three strata used in the randomisation of patients to treatment arms was also performed as a secondary analysis for PFS. • Exploratory analysis based on a Cox proportional hazards model, were conducted in order to assess the demographic and prognostic factors that most affected treatment outcome.
OS	• Time between randomisation and death (patients who died were considered to have had an event, regardless of the cause of death). • Patients who were lost to follow-up before the end of the trial or who were withdrawn from the trial were censored at the time of last contact. Patients who were still being treated were censored at the last available date the patient was known to be alive, or at the clinical cut-off date if it was earlier.	• OS was compared between treatment arms using an unstratified log-rank test with a two-sided significance level of 0.05. • The analysis of OS was based on all data available, including the survival data from the active treatment phase, PFS follow-up phase, and the long-term follow-up phase. • Exploratory analysis based on a Cox proportional hazards model, were conducted in order to assess the demographic and prognostic factors that most affected treatment outcome.
TTP	Time between the randomisation and disease progression based on the IMWG response criteria. Death was not	Analysed using the same method used for PFS.

	considered as an event. TTP was compared between treatment arms using the unstratified log-rank test.	
ORR	Number of confirmed responders (CR, VGPR and PR maintained for at least 6 weeks) divided by the number of patients in the ITT population for the primary analysis of response rate. ORR and the relative proportions in each response category were examined. Response categories were based on the IMWG criteria: CR, VGPR, PR, SD and PD. Confirmed responses documented after the patients received any other AMT were not counted as responses; however, these patients were included in the denominator.	Comparisons of ORR between treatment arms (2 × 2 table) were performed using a two-sided Fisher's exact test with a significance level of 0.05, together with 95% CIs. The distribution of patients over the five response categories (excluding the 'Response not evaluable') were compared between treatment arms using the Wilcoxon rank sum test (1 = CR, 2 = VGPR, 3 = PR, 4 = stable disease, 5 = PD).
DOR	Duration from the time when the response criteria were first met for CR, VGPR, or PR until the first date the response criteria were met for PD or until the subject died from any cause, whichever occurred first. Duration of response for subjects last known to be alive with no progression after a CR, VGPR, or PR were censored at the date of last adequate response assessment. Subjects with confirmed responses that occurred after receiving any other AMT, including radiation therapy initiated after baseline, were censored at the last adequate assessment before the initiation of such treatment. Subjects who were non-responders were excluded from this analysis.	Analysed using the same method used for PFS.
TTR	Time from randomisation to the time the response criteria for CR, VGPR, or PR were first met. Subjects who were non-responders were excluded from this analysis.	Summary statistics were used to summarise the time to response by treatment arm, and the time to response was compared between treatment arms using the Wilcoxon rank sum test, with subjects with the longest time to response having the highest rank.

TTF	Time between the randomisation and discontinuation of study treatment for any reason, including disease progression as determined by IMWG response criteria, treatment toxicity, start of another anti-myeloma treatment, and death. Subjects who had not discontinued the active treatment phase or the PFS follow-up phase at the time of analysis were censored on the date of last assessment.	Compared between treatment arms using the unstratified log-rank test. The same methods used for the PFS analysis were used.
PFS2	Time from randomisation to second objective PD, start of third-line therapy or death from any cause, whichever occurred first. Subjects alive and for whom a second objective PD had not been observed were censored at the last time known to be alive and without second objective PD.[67]	The same methods used for the PFS analysis were used.
HRQoL	HRQoL data were collected for the first 18 months of the trial and, given that the Rd and Rd18 arms were identical during this interval, HRQoL data for these two arms were pooled.[47]	Cross-sectional and longitudinal analyses and estimation of overall treatment effects were performed. Changes from baseline at each time point and at PD development were calculated for within-treatment and between-treatment comparisons. Change from baseline was tested for statistical significance using the one-sample *t*-test for within-treatment comparisons and using the two-sample *t*-test for between-treatment comparisons. Overall treatment effects of evaluated HRQoL domains at the population level were estimated using all longitudinal data points, mixed-model repeated measures analyses were performed using PROC MIXED in SAS® (SAS Institute Inc., Cary, NC, USA). The analyses used change in scores as the dependent variable and included baseline scores, time, treatment and treatment-by-time interaction as fixed effects; and intercept and time as random effects. A variance components covariance structure was used to model a different variance component for each random effect. The

		least-squares mean change from baseline within each treatment and the difference in least-squares mean change from baseline between treatments were estimated for each domain, based on the fixed effects.[47]

Key: AMT, anti-myeloma therapy; **CI**, confidence interval; **CR**, complete response; **HRQoL**, health-related quality of life; **IMWG**, International Myeloma Working Group; **IRAC**, Independent Response Adjudication Committee; **ITT**, intention-to-treat; **ORR**, overall response rate; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **PR**, partial response; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 18 cycles; **SD**, stable disease; **VGPR**, very good partial response.
Sources: Clinical Study Report CC-5013-MM-020/IFM 07-01[43] and Delforge et al., 2015.[47]

B.2.4.4 MM-020 participant flow

Figure 32, Appendix D presents a CONSORT image depicting patient flow in trial MM-020. Of the 2,030 patients screened, 407 were excluded for either not meeting inclusion criteria (n = 283) and/or meeting at least one exclusion criterion (n = 130). Between 29 August 2008 and 10 March 2011, 1,623 patients were enrolled and randomised in a 1:1:1 ratio to Rd (n = 535), Rd18 (n = 541) or MPT (n = 547).

Overall, fewer patients (86.5%) in the Rd group discontinued from the study (i.e. no longer receiving study treatment and also not in PFS follow-up phase) than in either the Rd18 (95.2%) or MPT (95.6%) groups. The most common reasons for study discontinuation were disease progression (50.7% with Rd, 66.9% with Rd18, 61.6% with MPT) and AEs (12.0% with Rd, 13.1% with Rd18, 13.9% with MPT). Up to the 21 January 2016 data cut-off, 52 patients (9.7%) were still receiving treatment in the Rd group. All patients in the Rd18 and MPT groups had either discontinued or completed 72 weeks of treatment. Fewer patients in the MPT group completed the full 72 weeks of study treatment (43.9%) than patients in the Rd18 group (51.9%).

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The quality assessment of study MM-020 is shown in Table 66 Appendix D. MM-020 is a high-quality study relevant to the decision problem.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 MM-020: summary of efficacy data

Table 14 summarises the key efficacy outcomes from study MM-020.

- Rd treatment produced statistically significantly better outcomes than MPT in terms of PFS (by IRAC and Investigator review, using either Food and Drug Administration [FDA] or EMA censoring rules), PFS2, DOR, TTR, ORR, TTF, TTP and time to second AMT. In addition, Rd treatment led to a statistically significantly longer OS compared with MPT and an associated 10 month improvement in OS.[31,43]
- The improved PFS with Rd is accompanied by an improvement in HRQoL. Relative to MPT, Rd demonstrated a significantly greater reduction in disease

symptoms and side effects of treatment. Rd also demonstrated consistent clinically meaningful improvement in utility on the 5-dimension European Quality of Life questionnaire (EQ-5D) at all post-baseline assessments except at month 1.[47]

- Depth of response (≥ very good partial response [VGPR]) was greater in patients who received Rd (48.6%) than in patients who received MPT (30.5%). In patients who had a best response of ≥ VGPR, the PFS and OS benefit of Rd over MPT was even more profound:
    - Median PFS of 52.5 months for arm Rd compared with 31.8 months for the MPT arm (HR 0.52; 95% CI: 0.40–0.66).[43]
    - Median OS of 79.5 months for arm Rd compared with 55.7 months for the MPT arm (HR 0.63; 95% CI: 0.48–0.83).[43]
- Rd treatment produced statistically significantly better outcomes than 18 cycles of Rd in terms of PFS (by IRAC and Investigator review using FDA and EMA censoring rules), DOR, TTF, TTP and time to second AMT.[31,43]

Table 14 Summary of key efficacy outcomes from study MM-020 (ITT population)

	Rd	MPT	Analysis
Randomised (n)	535	547	
Efficacy (n) (ITT population)	535	547	
Patients discontinuing study for any reason, n (%)	463 (86.5)	523 (95.6)	
Patients discontinuing study because of disease progression, n (%)	271 (50.7)	337 (61.6)	
Primary outcome			
Median PFS, months (24 May 2013 data cut-off)[a]	25.5	21.2	HR 0.72, 95% CI 0.61–0.85, $p = 0.00006$
Median PFS, months (24 May 2013 data cut-off, EMA censoring)[a]	27.3	23.4	HR 0.79, 95% CI 0.68–0.92, $p = 0.00210$
Median PFS, months (21 January 2016 data cut-off, FDA censoring)	26.0	21.9	HR 0.69, 95% CI 0.59–0.79, $p < 0.00001$
Median PFS, months (21 January 2016 data cut-off, EMA censoring)	26.5	23.0	HR 0.74, 95% CI 0.65–0.85, $p = 0.00001$
Selected secondary outcomes			
Median OS, months (21 January 2016 data cut-off)	59.1	49.1	HR 0.78, 95% CI 0.62–0.92, $p = 0.0023$
Median PFS2, months (21 January 2016 data cut-off)	42.9	35.0	HR 0.74, 95% CI 0.64–0.85, $p = 0.00003$
ORR (≥ PR), % (21 January 2016 data cut-off)	80.7	67.5	OR 2.02, (95% CI 1.53–2.68), $p < 0.00001$
Median TTP, months (21 January 2016 data cut-off)	31.3	24.4	HR 0.64, 95% CI 0.54–0.75, $p < 0.00001$
Median duration of response in patients achieving ≥ PR (21 January 2016 data cut-off)	31.5	22.1	HR 0.61, 95% CI 0.51–0.72, $p < 0.00001$

	Rd	MPT	Analysis
Median time to second-line AMT (21 January 2016 data cut-off)	36.7	26.7	HR 0.63, 95% CI 0.54–0.73, $p < 0.00001$

All results to the 24 May 2013 and 21 Jan 2016 data cut-offs were to a median follow up of 37 and 67 months, respectively. All data to 21 Jan 2016 data cut-off were assessed by investigator.

[a] IRAC assessment

Key: AMT, anti-myeloma treatment; **CI**, confidence interval; **EMA**, European Medicines Agency; **FDA**, Food and Drugs Administration; **HR**, hazard ratio; **ITT**, intent-to-treat; **MPT**, melphalan, prednisone and thalidomide; **NR**, not reported; **OR**, odds ratio; **ORR**, overall response rate; **OS**, overall survival; **PFS**, progression-free survival; **PFS2**, time from initial randomisation to second objective disease progression, start of third-line therapy or death from any cause; **PR**, partial response; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **TTP**, time to progression.

Source: Clinical Study Report CC-5013-MM-020/IFM 07-01;[43] except PFS (EMA) censoring data (updated data tables).[68]

B.2.6.2 MM-020 overview

In this section, efficacy results are presented by data cut-off. The primary endpoint analysis for PFS, as at the 24 May 2013 data cut-off, was published in the New England Journal of Medicine for a median follow-up of 37 months.[31] As described earlier (see section B.2.3.5), for this cut-off, response data were independently verified and were used for the primary endpoint analysis of PFS; for OS, this was a planned interim analysis.[31,43]

The second analysis included in this section is from an updated data cut-off on 21 January 2016 representing a median of 67.0 months follow-up.[43]

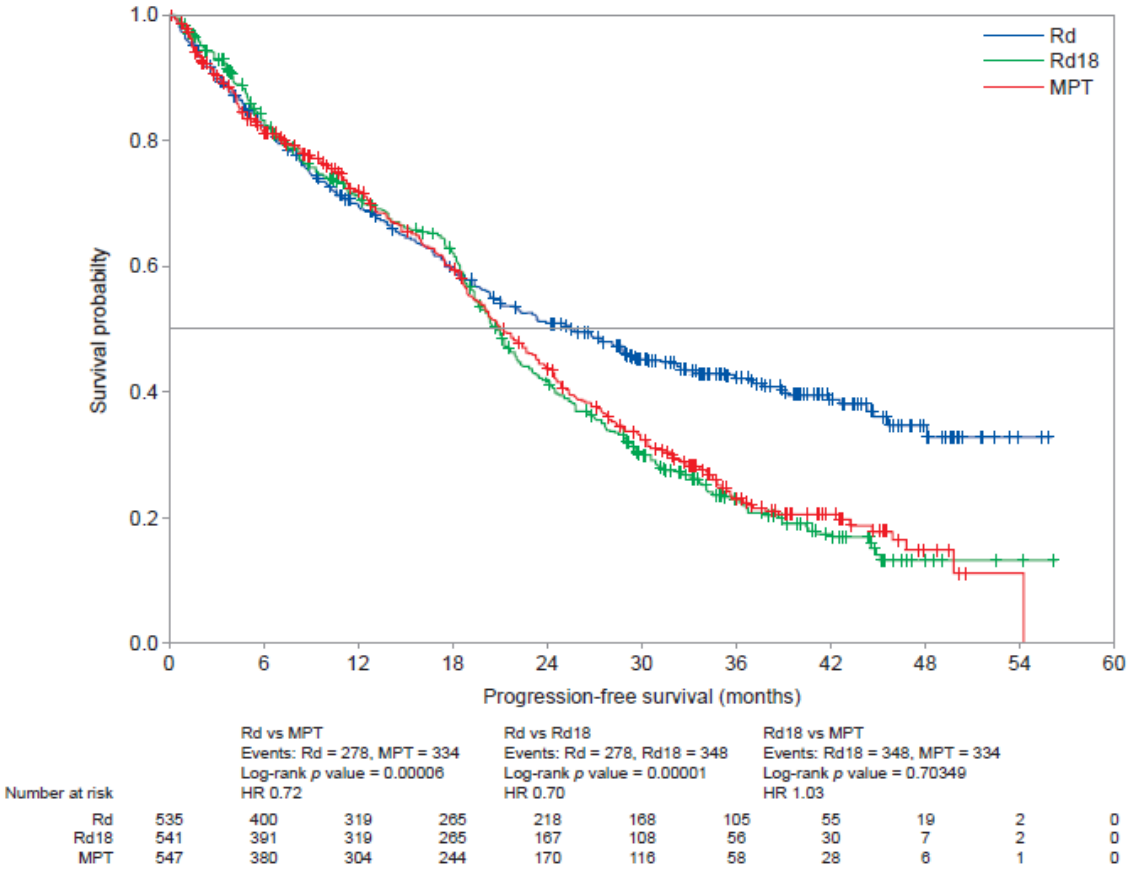
B.2.6.3 MM-020 progression-free survival

PFS results: IRAC assessment, (FDA censoring criteria), 24 May 2013 data cut-off (primary end-point)

Final PFS data for study MM-020 demonstrate that Rd until disease progression was a more effective regimen than administration of MPT therapy for a set duration of 72 weeks. At the planned 24 May 2013 analysis, the required number of events had been surpassed, allowing the final PFS analysis. Figure 3 shows Kaplan–Meier estimates of PFS based on the IRAC review for the primary comparison between Rd and MPT.

The primary outcome analysis showed a 28% reduction in the risk of disease progression or death with Rd compared with MPT given for 72 weeks. (hazard ratio [HR] 0.72; 95% confidence interval [CI] 0.61–0.85; $p = 0.00006$). The difference in median PFS between Rd (25.5 months) and MPT (21.2 months) was 4.3 months. At 4 years, 35% of patients receiving Rd, compared with 15% receiving MPT, remained event-free.[43]

Figure 3 Kaplan–Meier plots of PFS (based on IRAC review using IMWG criteria) for MM-020 (ITT population, FDA censoring rules)



Data cut-off date = 24 May 2013.
Horizontal line indicates the median; short vertical lines on each curve indicate patients with censored data.
Key: FDA, Food and Drugs Administration; **HR**, hazard ratio; **IMWG**, International Myeloma Working Group; **IRAC**, Independent Response Adjudication Committee; **ITT**, intent-to-treat; **MPT**, melphalan, prednisone and thalidomide; **PFS**, progression-free survival; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 18 cycles.
Source: Clinical Study Report CC-5013-MM-020/IFM 07-01.[43]

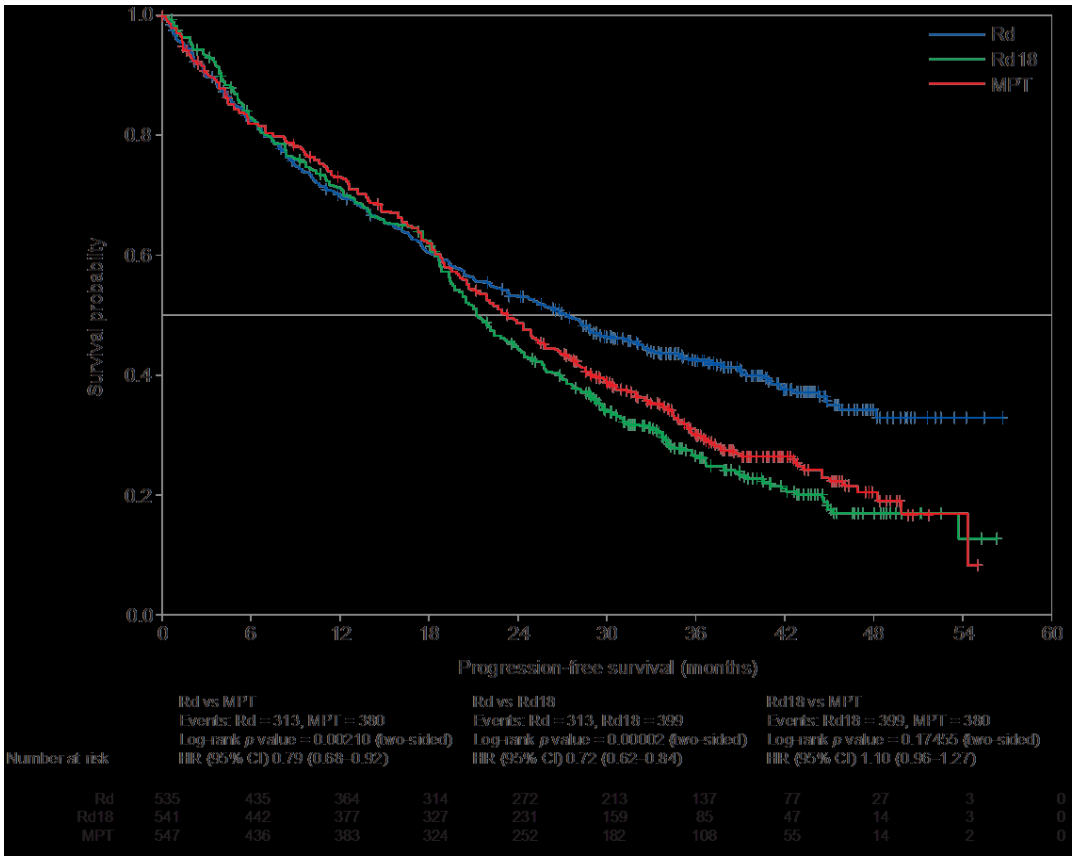
The secondary PFS comparison between Rd and Rd18 showed a 30% reduction in the risk of disease progression or death with Rd (HR 0.70; 95% CI 0.60–0.82) compared with the same therapy given for a set duration of 72 weeks. PFS was significantly longer in the Rd group compared with Rd18 (p = 0.00001). At 4 years, 35% of patients receiving Rd compared with 13% receiving Rd18 remained event-free.

PFS results: IRAC assessment, (sensitivity analysis using EMA censoring criteria), 24 May 2013 data cut-off

A sensitivity analyses for PFS was performed to support the robustness of the primary PFS results. As the original IRAC reviewed PFS endpoint was analysed using censoring rules based on 2007 FDA guidance,[63] this same data was then re-analysed using censoring rules based on 2012 EMA guidance[67] in which PFS was defined as the time from randomisation to objective disease progression or to death from any cause. All progressions and deaths were considered as events, regardless of whether they occurred after initiating other AMT or after 2 or more missed scheduled assessments. Subjects alive and for whom an objective disease progression had not been observed were censored at the last time known to be alive. Other censoring rules specified in Table 13 were still followed (see Appendix C, Table 55 for full details).

The sensitivity analysis using EMA censoring rules (Figure 4) was consistent with the PFS analysis using FDA censoring rules. Rd significantly improved PFS as compared with MPT given for 72 weeks (HR 0.79; 95% CI 0.68–0.92; p = 0.00210).[43,68]

Figure 4 Kaplan–Meier plots of PFS (based on IRAC review using IMWG criteria) for MM-020 (ITT population, EMA censoring criteria)

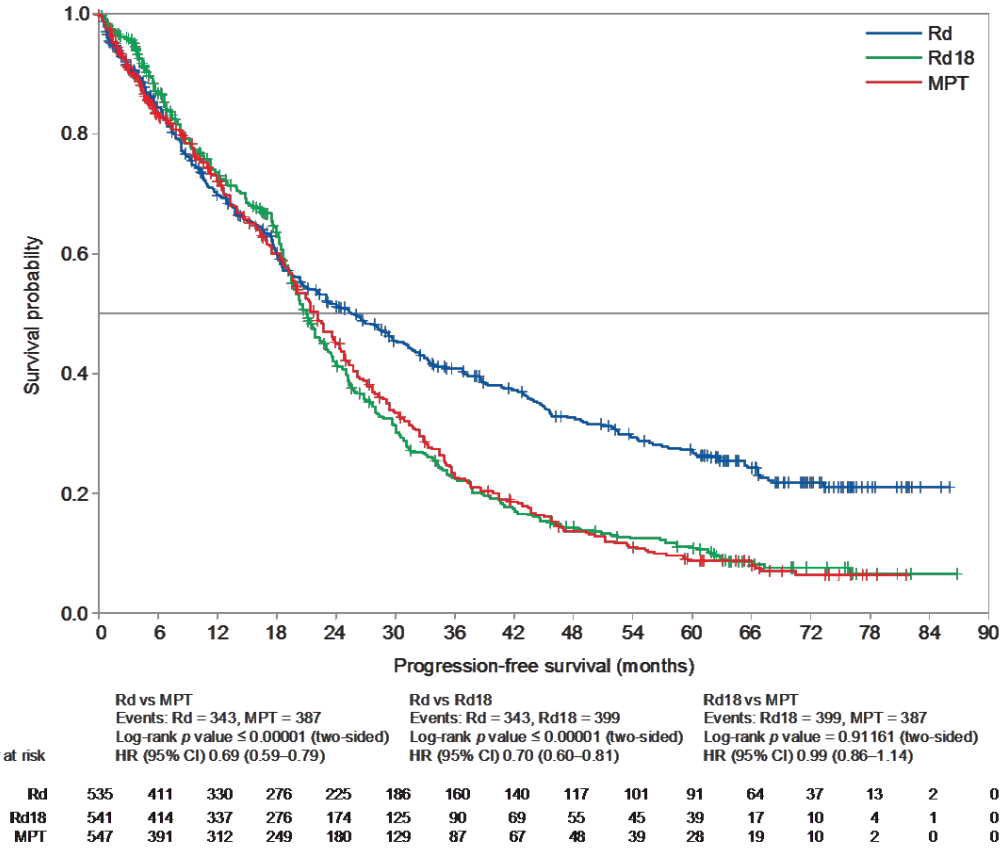


Data cut-off date = 24 May 2013.
Horizontal line indicates the median; short vertical lines on each curve indicate patients with censored data.
Key: CI, confidence interval; **EMA**, European Medicines Agency; **HR**, hazard ratio; I**MWG**, International Myeloma Working Group; **IRAC**, Independent Response Adjudication Committee; **ITT**, intent-to-treat; **MPT**, melphalan, prednisone and thalidomide; **PFS**, progression-free survival; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 18 cycles.
Source: Clinical Study Report CC-5013-MM-020/IFM 07-01.[43,68]

PFS results, investigator assessment, 21 January 2016 data cut-off

Updated PFS results by investigator assessment using IMWG criteria (using FDA censoring rules) based on the later 21 January 2016 data cut off (Figure 5) were consistent with those based on IRAC and investigator at the earlier 24 May 2013 data cut off. The risk of disease progression or death was reduced with Rd compared with MPT (HR 0.69; 95% CI 0.59–0.79; $p < 0.00001$) and Rd18 (HR 0.70; 95% CI 0.60–0.81; $p < 0.00001$).[43] The median PFS was Rd (26 months), Rd 18 (21 months) and MPT (21.9 months). At 5 years, 27% of patients receiving Rd compared to 11% receiving Rd18 and 9% receiving MPT remained event-free.

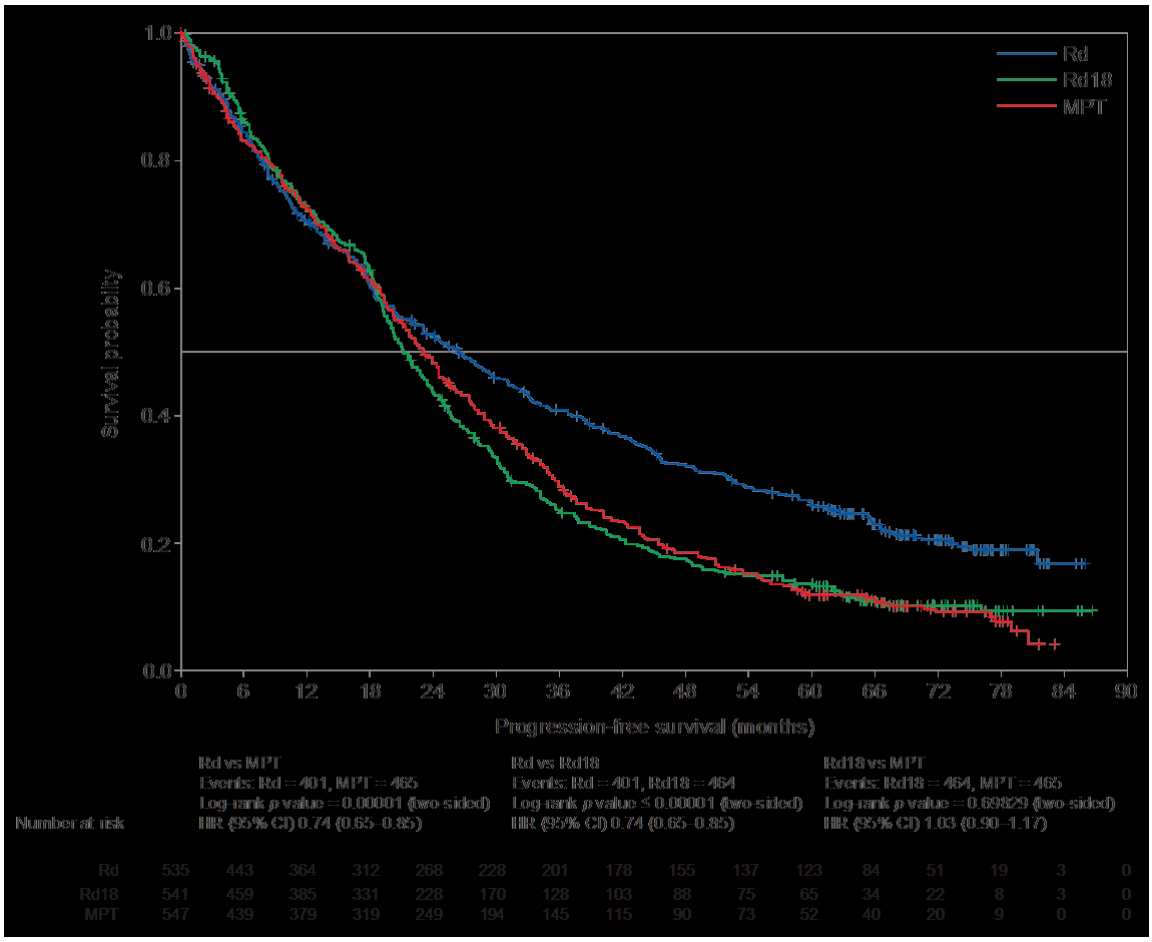
Figure 5 Kaplan–Meier plots of PFS (investigator review using IMWG criteria) for MM-020 (ITT population, FDA censoring criteria)



Data cut-off date = 21 January 2016.
Horizontal line indicates the median; short vertical lines on each curve indicate patients with censored data.
Key: CI, confidence interval; **FDA**, Food and Drugs Administration; **HR**, hazard ratio; I**MWG**, International Myeloma Working Group; **ITT**, intent-to-treat; **MPT**, melphalan, prednisone and thalidomide; **PFS**, progression-free survival; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 18 cycles.
Source: Clinical Study Report CC-5013-MM-020/IFM 07-01.[43,68]

Similarly, when these data were analysed using EMA censoring rules, the Rd advantage over both MPT and Rd18 was still evident (Figure 6). The risk of disease progression or death was reduced with Rd compared with MPT (HR 0.74; 95% CI 0.65–0.85; p = 0.00001) and Rd18 (HR 0.74; 95% CI 0.65–0.85; p = 0.00001).

Figure 6 Kaplan–Meier plots of PFS (investigator review using IMWG criteria) for MM-020 (ITT population, EMA censoring criteria)



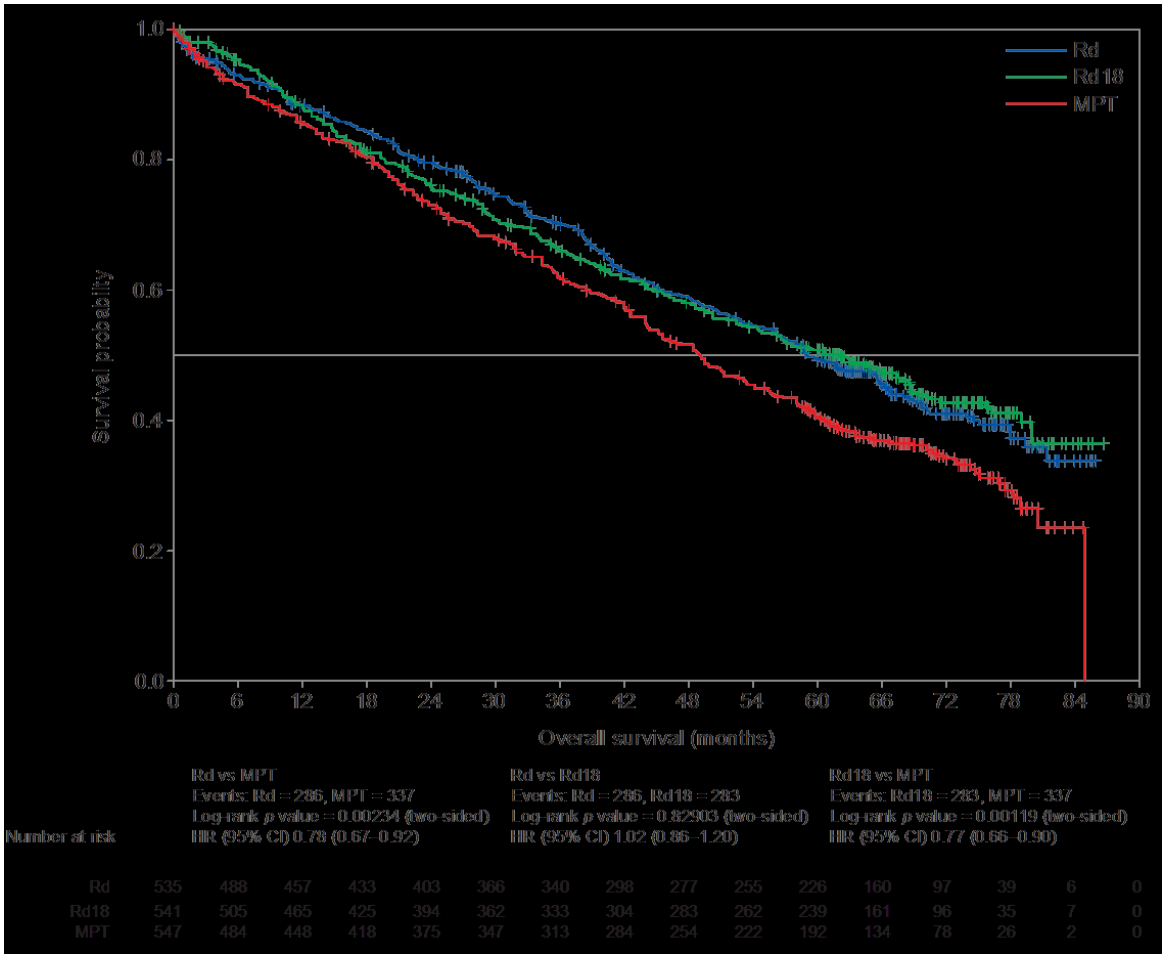
Data cut-off date = 21 January 2016.
Horizontal line indicates the median; short vertical lines on each curve indicate patients with censored data.
Key: CI, confidence interval; **EMA**, European Medicines Agency; **HR**, hazard ratio; I**MWG**, International Myeloma Working Group; **ITT**, intent-to-treat; **MPT**, melphalan, prednisone and thalidomide; **PFS**, progression-free survival; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 18 cycles.
Source: Clinical Study Report CC-5013-MM-020/IFM 07-01.[43,68]

B.2.6.4 MM-020 overall survival

For the final analysis of OS (21 January 2016 data cut-off,) the median follow-up time for all surviving patients was 67.0 months.[43] There were 906 deaths across the treatment groups (56% [906/1623] of the ITT population, which represented 100% study information (896 pre-specified events for the final OS analysis). For the comparison of Rd versus MPT, there were a total of 623 events across the treatment groups (58% [623/1082] which represented 100% information (597 pre-specified events for the final OS analysis).

Treatment with Rd was associated with statistically significant improvement in OS relative to MPT (Figure 7). Median OS was 59.1 months with Rd compared with 49.1 months with MPT, representing a 10.0 month improvement (HR 0.78; 95% CI 0.67–0.92; log-rank test $p = 0.002$). The estimated 5-year OS rates were 49% with Rd and 41% with MPT.[43]

Figure 7 Kaplan–Meier plots of final OS for MM-020 (ITT population)



Data cut-off date = 21 January 2016
Horizontal line indicates the median; short vertical lines on each curve indicate patients with censored data.
Key: CI, confidence interval; **HR**, hazard ratio; **ITT**, intent-to-treat; **MPT**, melphalan, prednisone and thalidomide; **OS**, overall survival; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 18 cycles.
Source: Clinical Study Report CC-5013-MM-020/IFM 07-01.[43]

B.2.6.5 MM-020 progression-free survival on next-line therapy (PFS2), post hoc analysis

Median PFS2 was longer in patients treated first-line with Rd (42.9 months) relative to those treated with MPT (35.0 months), a difference of 7.9 months ($p = 0.00003$). Full details of the PFS2 outcome analysis can be found in Appendix L.

B.2.6.6 MM-020 myeloma response rates

Treatment with Rd was associated with a higher ORR compared with MPT. As of the 21 January 2016 data cut-off, 80.7% of patients receiving Rd responded (≥ partial response [PR]) as compared with 67.5% of patients receiving MPT ($p < 0.00001$). The proportion of patients with complete response (CR) or VGPR indicated a deeper quality of response to therapy with Rd (48.6%) than with MPT (30.5%). Response data are summarised in Table 15.

Table 15 Myeloma response rates (investigator assessment; ITT population for MM-020)

	Rd (n = 535)	Rd18 (n = 541)	MPT (n = 547)
Response[a], n (%)			
CR + VGPR	260 (48.6)	255 (47.1)	167 (30.5)
CR	119 (22.2)	110 (20.3)	68 (12.4)
VGPR	141 (26.4)	145 (26.8)	99 (18.1)
PR	172 (31.6)	170 (31.4)	202 (36.9)
SD	66 (12.3)	83 (15.3)	116 (21.2)
PD	10 (1.9)	6 (1.1)	17 (3.1)
NE[b]	27 (5.0)	27 (5.0)	45 (8.2)
Dichotomized response			
CR, VGPR or PR	432 (80.7)	425 (78.6)	369 (67.5)
SD, PD or NE[b]	103 (19.3)	116 (21.4)	178 (32.5)
Comparison between treatment arms			
Rd vs MPT (odds ratio, *p* value[c])	2.02 (95% CI 1.53–2.68), $p < 0.00001$		
Rd vs Rd18 (odds ratio, *p* value[c])	1.14 (95% CI 0.85–1.54), $p = 0.40500$		
Rd18 vs MPT (odds ratio, *p* value[c])	1.77 (95% CI 1.35–2.32), $p = 0.00004$		

Data cut-off date = 21 January 2016.
[a] Best response of a patient.
[b] Including patients who did not have any response assessment data, or NE.
[c] From Fisher's exact test with normal approximation.
Key: CI, confidence interval; **CR**, complete response; **ITT**, intent to treat; **MPT**, melphalan, prednisone and thalidomide; **NE**, not evaluable; **PD**, progressive disease; **PR**, partial response; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 18 cycles; **SD**, stable disease; **VGPR**, very good partial response.
Source: Clinical Study Report CC-5013-MM-020/IFM 07-01.[43]

B.2.6.7 MM-020 duration of response and time to response

Among responders to treatment (≥ PR, see Table 15), response was faster and more durable in the Rd group than the MPT group. Using the 21 January 2016 data cut-

off, the median time to first response was 1.8 months with Rd and 2.8 months with MPT.[43] Furthermore, duration of response was longer for patients treated with Rd (31.5 months) compared with those treated with MPT (22.1 months; HR 0.61; 95% CI 0.51–0.72; $p < 0.00001$), see also Appendix L.

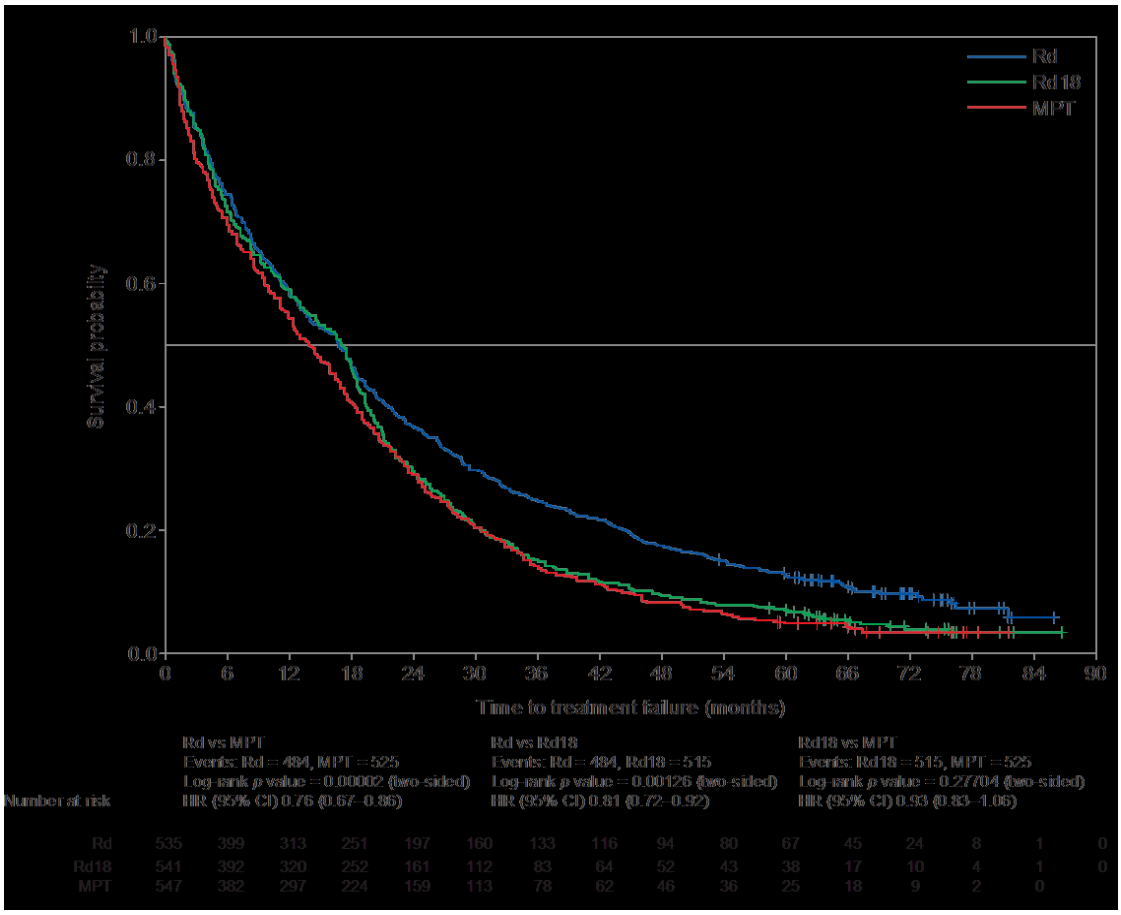
B.2.6.8 MM-020 time to progression

Analysis of TTP by investigator based on IMWG criteria was consistent with the PFS results, showing notable differences between the treatment groups in favour of Rd. Using the 21 January 2016 data cut-off, the TTP analysis indicates a 36% reduction in the risk of disease progression for patients treated with Rd compared with those treated with MPT (HR 0.64; 95% CI 0.54–0.75). The median TTP with Rd was 31.3 months, compared with 24.4 months with MPT (a difference of 6.9 months; $p < 0.00001$). At 5 years, 33.5% of patients receiving Rd and 10.4% of patients receiving MPT remained event-free.[43,68]

B.2.6.9 MM-020 time to treatment failure

Analysis of TTF was consistent with PFS, showing notable differences in favour of Rd. Using the 21 January 2016 data cut-off, Rd was associated with a 24% reduction in the risk of discontinuing study treatment for any reason compared with MPT (HR 0.76; 95% CI 0.67–0.86). The TTF was longer in the Rd group (16.9 months) than in the MPT group (14.1 months; $p = 0.00002$).[43] The Kaplan–Meier curve shows clear and superior benefits of Rd versus MPT in controlling the disease and consequently delaying time to treatment failure (Figure 8).[43] It is noteworthy that in the TTF analysis, the Kaplan–Meier curves for Rd (treatment continued until disease progression) and for Rd18 (treatment duration 72 weeks) overlap until around 18 months, while the MPT (treatment duration 72 weeks) curve separates at an earlier time point.

Figure 8 Kaplan–Meier plots of TTF (based on investigator assessment; ITT population for MM-020)



Data cut-off date = 21 January 2016.
Horizontal line indicates the median; short vertical lines on each curve indicate patients with censored data.
Key: CI, confidence interval; **HR**, hazard ratio; **ITT**, intent to treat; **MPT**, melphalan, prednisone and thalidomide; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 18 cycles; **TTF**, time to treatment failure.
Source: Clinical Study Report CC-5013-MM-020/IFM 07-01.[43,68]

B.2.6.10 MM-020 time to second-line therapy

Using the 21 January 2016 data cut-off, the median time to second-line AMT was significantly longer with Rd (36.7 months) than with MPT (26.7 months; HR 0.63; 95% CI 0.54–0.73; log-rank test $p < 0.00001$).[43] At 5 years after randomisation, 82% of patients who initially received MPT had gone on to receive a second-line therapy compared with 64% of patients in the Rd group. These data support the argument that Rd helps to provide more tolerable and sustained disease control, delaying the need for a second anti-myeloma regimen. This could be particularly beneficial for older patients who may not have the opportunity or capacity to receive multiple lines of treatment.

B.2.6.11 MM-020 health-related quality of life

Patient-reported outcome measures were used to determine if the choice of initial therapy resulted in differences over time in symptom burden and HRQoL. Data were collected for a maximum of 18 months (to data cut-off 24 May 2013) or until progressive disease (PD) developed using the myeloma-specific European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Multiple Myeloma 20 (EORTC QLQ-MY20), the general oncology-related EORTC Quality of Life Questionnaire – Core 30 (QLQ-C30) and the generic EQ-5D-3L. For the purpose of this HRQoL analysis, and because the Rd and Rd18 regimens were identical over the first 18 months of the study, the data from the two groups were collated into one "Rd" group in a *post hoc* fashion.[47]

Patients completed questionnaires at several time points, at baseline, at the end of cycles 1, 3, 6, 12 and 18, and at study discontinuation. Recording was stopped at 18 cycles as the aim was to make a direct comparison between Rd and MPT over the same time period, this approach was essential to avoid bias from subsequent treatments. To try to answer whether HRQoL is maintained in the long term, an exploratory analysis was undertaken to look for trends in AEs during up to 2 years of treatment. The analysis did not show an increase in incidence of AEs during months 18–24, suggesting that, from the perspective of side effects, HRQoL does not deteriorate beyond 18 months of treatment.

The main HRQoL analysis focused on six pre-selected and clinically relevant HRQoL domains – two from the QLQ-MY20 (Disease Symptoms and Side Effects of Treatment) and four from the QLQ-C30 (Global Health Status, Physical Functioning, Fatigue, and Pain) and the EQ-5D utility value. These domains were chosen before data analysis, following a workshop discussion with haematologists, and based on perceived clinical relevance.

Cross-sectional and longitudinal HRQoL analysis and estimation of overall treatment effects were performed (24 May 2013 data cut off). In order to assess if statistical differences translated into clinically meaningful improvements/differences, the minimal important difference (MID) associated with each domain was considered. MM-specific MIDs were applied to the QLQ-C30 and QLQ-MY20 domains: Global Health Status (MID = 7); Physical Functioning (MID = 9); Pain (MID = 12); Fatigue

(MID = 10); Disease Symptoms (MID = 10) and Side Effects of Treatment (MID = 6). The Walters and Brazier MID of 0.07 was applied to the EQ-5D utility. Rigorous MID methods, in which the mean and 95% CIs of change must meet the MID, were applied.

Compliance with the questionnaires was similar between treatment arms at the end of the first treatment cycle, and after 3 and 6 months (≥ 84%); however, at months 12 and 18, compliance rates were lower among patients randomised to MPT than to Rd. At study discontinuation, there was no statistical difference between groups, compliance rates stood at 53–59% in both treatment arms.

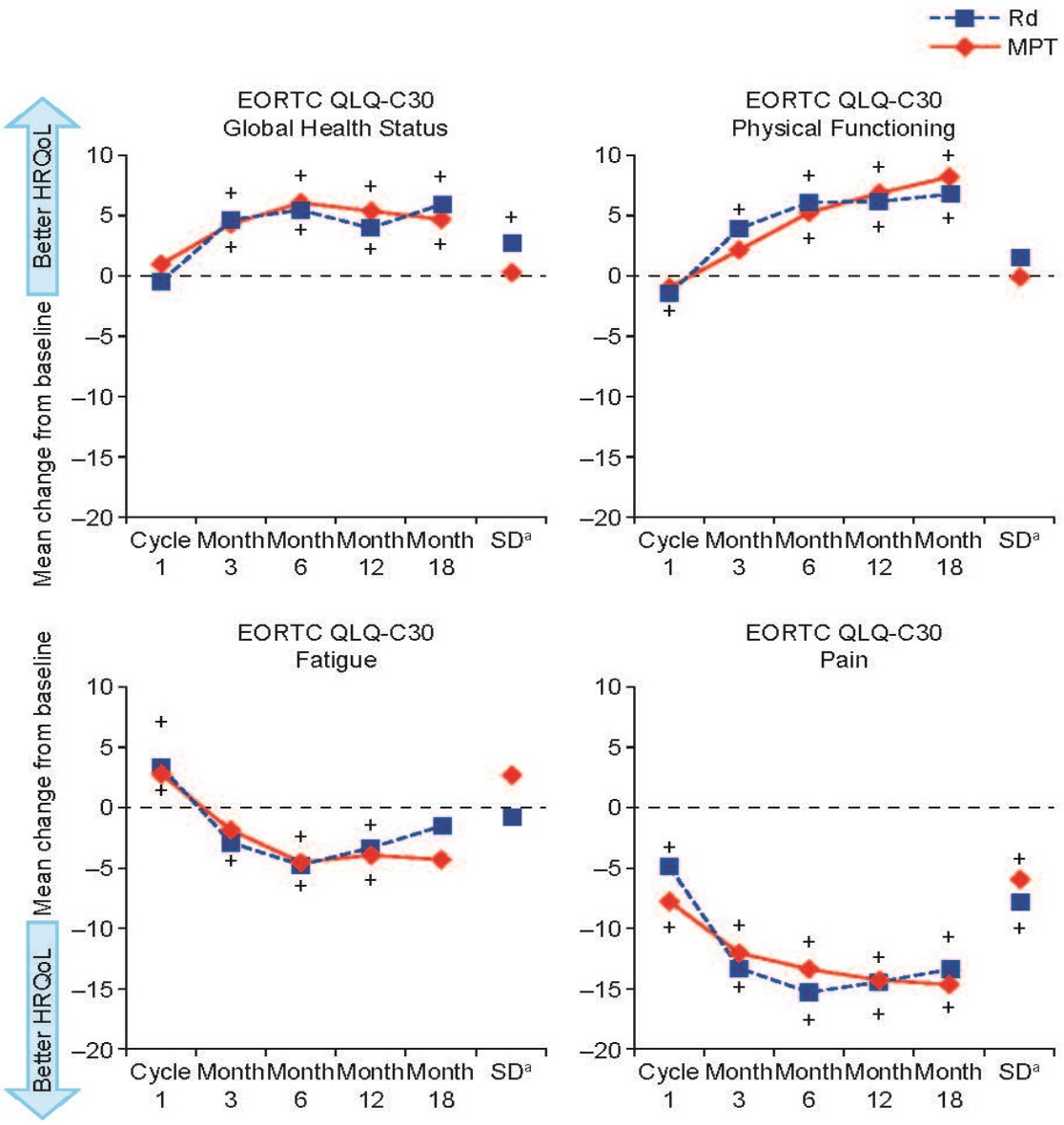
Both Rd and MPT led to statistically significant symptom relief. Rd and MPT showed statistically significant ($p < 0.05$) reductions in pain (QLQ-C30 Pain and QLQ-MY20 Disease Symptoms domains) at all post-baseline assessments (Figure 9 and Figure 10). However, when the MID score of 12 for Pain was applied, Rd demonstrated clinically meaningful improvement at months 6 and 12, compared to MPT. Further, Rd demonstrated a significantly greater reduction in QLQ-MY20 Disease Symptoms compared with MPT at month 3 ($p = 0.04$), and an overall lower symptom score across all assessments (Figure 10). The Rd group also showed significant improvement in Fatigue from baseline at month 3, month 6 and month 12 (Figure 9).

Although Rd and MPT showed worsening in the QLQ-MY20 Side Effects of Treatment domain, the Rd group showed consistently lower scores, indicating fewer or less severe side effects, across all post-baseline assessments, with all but month 18 being statistically significantly ($p < 0.05$) lower than the MPT group (Figure 10). The Side Effects of Treatment domain narrowly missed being clinically significant in favour of Rd compared with MPT when a MID of 6 was applied: the MPT maximum score was 5.6, compared with 3.3 with Rd.[47]

Both Rd and MPT improved patients' HRQoL from baseline over the duration of the study across all pre-selected domains of the questionnaires, but HRQoL dropped at progression. Statistically significant improvements ($p < 0.05$) from baseline were observed for Rd and MPT for functional scales Global Health Status, Physical Functioning, and EQ-5D utility (Figure 9 and Figure 10) at all time points after the first cycle, however no significant differences were reported between treatment arms.

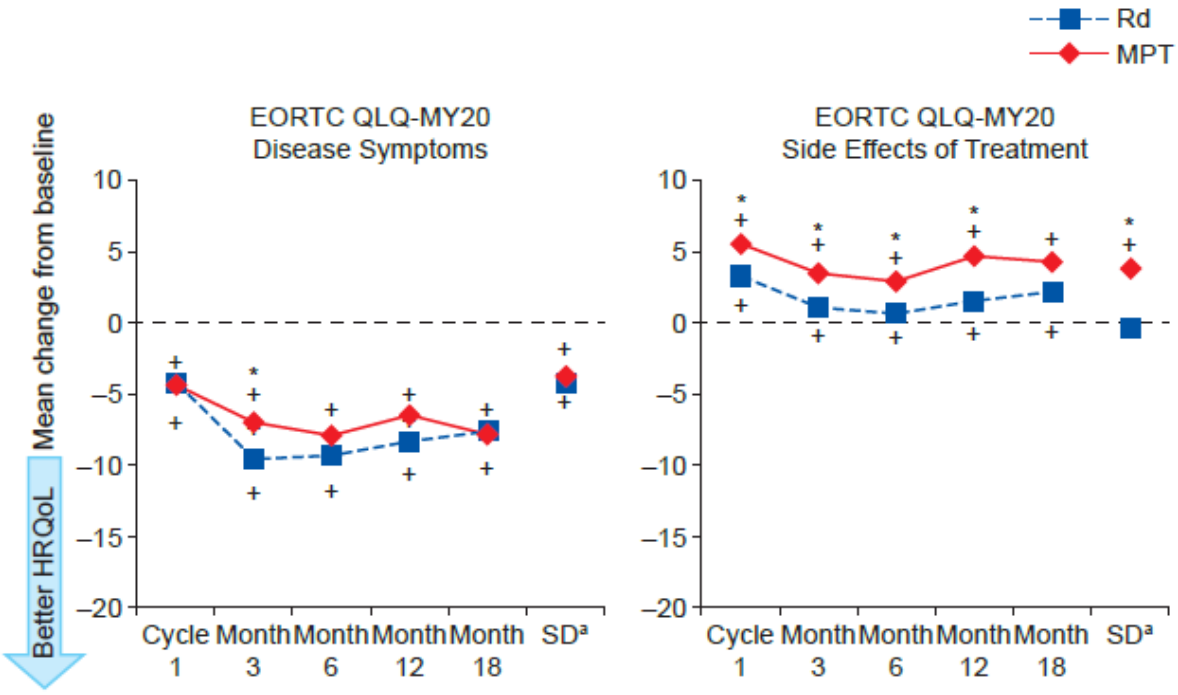
The Rd group demonstrated consistent clinically meaningful improvement in HRQoL as measured by EQ-5D at all post-baseline assessments except at month 1. The MPT group only demonstrated clinically meaningful improvement at month 3.[47]

Figure 9 Cross-sectional analysis of mean QLQ-C30 change from baseline per assessment visit and at study discontinuation in the Rd and MPT groups for MM-020



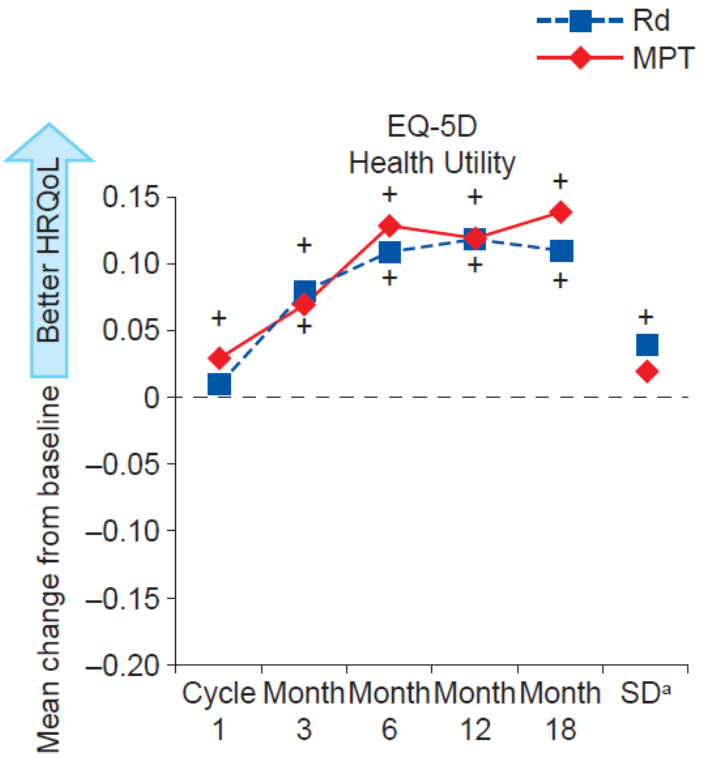
+ Significant within-group change from baseline ($p < 0.05$, 1-sample *t*-test).
* Significant between-group difference in change from baseline ($p < 0.05$, 2-sample *t*-test).
[a] Stable disease can occur at any time point.
Key: EORTC, European Organisation for Research and Treatment of Cancer; **HRQoL**, health-related quality of life; **MPT**, melphalan, prednisone and thalidomide; **QLQ-C30**, Quality of Life Questionnaire – Core 30; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **SD**, stable disease.
Source: Delforge *et al.* 2015.[47]

Figure 10 Cross-sectional analysis of mean QLQ-MY20 change from baseline per assessment visit and at study discontinuation in the Rd and MPT groups for MM-020



[+] Significant within-group change from baseline ($p < 0.05$, 1-sample *t*-test).
* Significant between-group difference in change from baseline ($p < 0.05$, 2-sample *t*-test).
[a] Stable disease can occur at any time point.
Key: EORTC, European Organisation for Research and Treatment of Cancer; **HRQoL**, health-related quality of life; **MPT**, melphalan, prednisone and thalidomide; **QLQ-MY20**, Quality of Life Questionnaire–Multiple Myeloma module; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **SD**, stable disease.
Source: Delforge *et al.* 2015.[47]

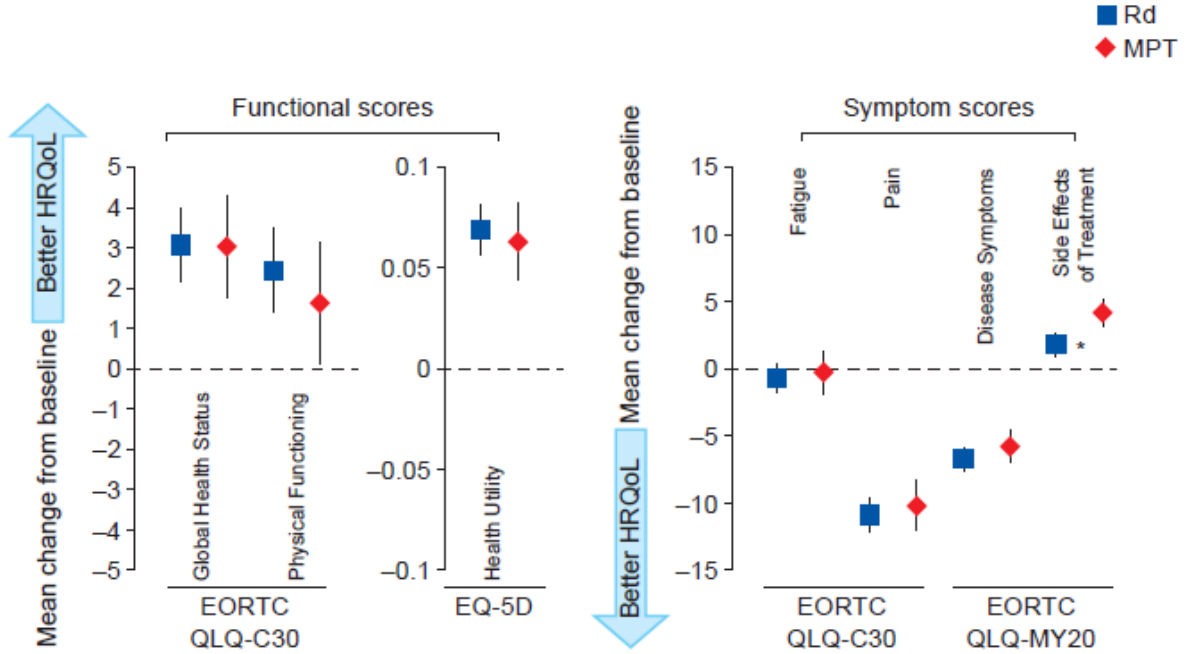
Figure 11 Cross-sectional analysis of mean EQ-5D change from baseline per assessment visit and at study discontinuation in the Rd and MPT groups for MM-020



[+] Significant within-group change from baseline ($p < 0.05$, 1-sample *t*-test).
*Significant between-group difference in change from baseline ($p < 0.05$, 2-sample *t*-test).
[a] Stable disease can occur at any time point.
Key: EQ-5D, 5-dimension European Quality of Life questionnaire; **HRQoL**, health-related quality of life; **MPT**, melphalan, prednisone and thalidomide; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **SD**, stable disease.
Source: Delforge *et al.* 2015.[47]

The results of the linear mixed-model repeated measures analyses confirmed those observed in the cross-sectional analysis. Significant within-treatment improvements over time were observed in both treatment arms in all domains except Fatigue and Side Effects of Treatment (Figure 12). A significant ($p < 0.0001$) between-group difference in mean change from baseline was observed for the Side Effects of Treatment domain in favour of Rd, indicating fewer severe side effects than the MPT group (Figure 13).[47]

Figure 12 Linear mixed-model repeated-measures analysis of mean change from baseline at 18 months in the Rd and MPT groups for MM-020

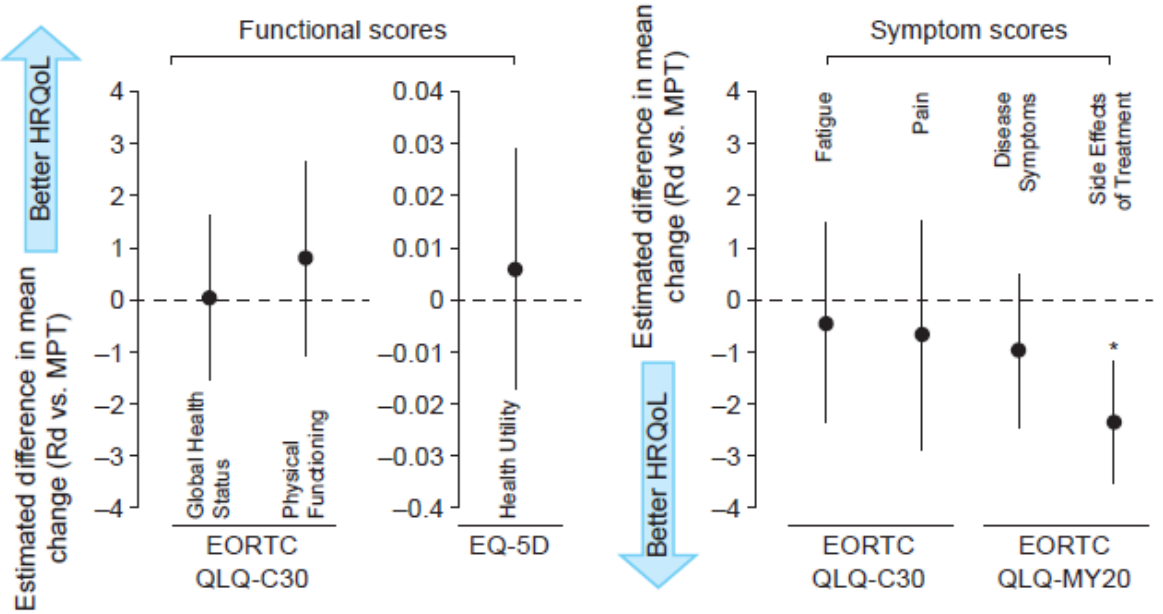


*$p < 0.05$.

Key: EORTC, European Organisation for Research and Treatment of Cancer; **EQ-5D**, 5-dimension European Quality of Life questionnaire; **HRQoL**, health-related quality of life; **MPT**, melphalan, prednisone and thalidomide; **QLQ-C30**, Quality of Life Questionnaire – Core 30, **QLQ MY20**, Quality of Life Questionnaire – Multiple Myeloma module; **Rd**, lenalidomide and low-dose dexamethasone until disease progression.

Source: Delforge *et al.* 2015.[47]

Figure 13 Linear mixed-model repeated-measures analysis of mean difference in change from baseline at 18 months in the Rd and MPT groups for MM-020



*$p < 0.05$.

Key: EORTC, European Organisation for Research and Treatment of Cancer; **EQ-5D**, 5-dimension European Quality of Life questionnaire; **HRQoL**, health-related quality of life; **MPT**, melphalan, prednisone and thalidomide; **QLQ-C30**, Quality of Life Questionnaire – Core 30, **QLQ MY20**, Quality of Life Questionnaire–Multiple Myeloma module; **Rd**, lenalidomide and low-dose dexamethasone until disease progression.

Source: Delforge *et al.* 2015.[47]

Taken together, these data show that the improved PFS with Rd is accompanied by an improvement in HRQoL, showing both statistically significant and clinically meaningful changes from baseline. Rd showed statistical superiority to MPT in Side Effects of Treatment, and no evidence of inferiority to MPT in any of the pre-selected HRQoL domains. This finding is of importance because it demonstrates that the improved PFS in this study does not come at a cost of decreased HRQoL.[47]

B.2.6.12 MM-020: subsequent anti-myeloma therapies (*post hoc* analysis)

By the time of the 21 January 2016 data cut, a lower proportion of patients in the Rd arm (56%) had received any salvage AMT compared to those in the Rd18 or MPT arms (70% each). A summary of subsequent therapy by treatment arm is presented in Table 16).

Table 16 Number of patients who received salvage therapy by type of drugs in all regimens (ITT population, study MM-020)

Salvage Therapy Patients who received —	**Rd (N = 535) n (%)**	**Rd18 (N = 541) n (%)**	**MPT (N = 547) n (%)**
Any salvage therapy[a]	299 (55.9)	377 (69.7)	381 (69.7)
Lenalidomide[b]	75 (25.1)	141 (37.4)	264 (69.3)
Bortezomib/carfilzomib[b]	236 (78.9)	283 (75.1)	277 (72.7)
Thalidomide[b]	67 (22.4)	63 (16.7)	38 (10.0)
Glucocorticoid[b,c]	277 (92.6)	357 (94.7)	357 (93.7)
Alkylating agents[b,d]	213 (71.2)	245 (65.0)	188 (49.3)
Other therapies [b]	93 (31.1)	108 (28.6)	99 (26.0)

[a] Percentages were based on the ITT population.
[b] Percentages were based on the number of subjects who received any salvage therapy.
[c] Included betamethasone, deltison, dexamethasone, methylprednisolone, prednisolone, prednisone, and corticosteroid.
[d] Included betamethasone, carmustine, cyclophosphamide, fotemustine, melphalan, chlorambucil, busulfan, dihydroxybusulfan, mechlorethamine, lomustine, semustine, dacarbazine, cisplatin, and carboplatin.
Key: ITT, intent to treat; **MPT**, melphalan, prednisone and thalidomide; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, 18 cycles of lenalidomide and low-dose dexamethasone.
Source: Clinical Study Report CC-5013-MM-020/IFM 07-01.[43]

B.2.7 Subgroup analysis

B.2.7.1 MM-020 stratification factors

Selected pre-planned subgroup analyses were performed comparing the different treatment regimens in terms of PFS, PFS2, OS and myeloma response outcomes. The following pre-planned subgroups were analysed based on stratification factors:

- Age group (≤ 75 years, > 75 years)
- Baseline ISS disease stage (stages I or II, stage III)
- Geographical region: data grouped into three regions for analysis according to clinical practice: North America and Pacific Region (USA, Canada, Australia and New Zealand), Europe (Austria, Belgium, France, Germany, Greece, Italy, Portugal, Spain, Sweden, Switzerland and UK) and Asia (China, Taiwan and Republic of Korea).

B.2.7.2 MM-020 additional pre-planned subgroup analysis

Pre-planned subgroup analysis (PFS, PFS2 OS and myeloma response outcomes) was also performed for the following groups:

- Sex (male, female)
- Race (White or Caucasian, Asian, other)
- Parameters of prognostic significance (e.g. baseline cytogenetic categories (high risk versus non-high risk: non-high risk was patients with favourable hyperdiploidy, normal, and uncertain risk cytogenetic risk profiles) and baseline renal function (≥ 80 mL/min, ≥ 50 mL/min, ≥ 30 mL/min, < 30 mL/min).

B.2.7.3 MM-020 statistical methods for subgroup analysis

Each subgroup was evaluated separately using analysis methods described for the primary and secondary efficacy outcomes. If too few patients fell into any subgroup, analysis within that subgroup may not have been performed or alternative cut-off points may have been considered. Details of statistical analyses undertaken in MM-020 are described earlier (Table 13).

B.2.7.4 MM-020 PFS analysis by subgroup

PFS was evaluated in a variety of subgroups (including the three stratification factors, as well as subgroups defined by sex, race, CrCl, baseline albumin, lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group (ECOG) performance status, and cytogenetic risk profile examined and parameters of prognostic significance). The results, illustrated as a Forest plot in Appendix E, Figure 33, were consistent with primary ITT analysis showing a benefit for Rd over MPT in the majority of subgroups, except for those with too few patients (e.g. LDH levels ≥ 200 U/L and Asian race).

A table of PFS by age and ISS stage (investigator assessment, 21 Jan 2016 cut-off) can be found in Appendix E, Table 68.

B.2.7.4.1 PFS based on response (post hoc analysis)

A secondary analysis was conducted to look at PFS outcomes by depth of response. There were 260 patients in arm Rd, and 167 subjects in arm MPT with a best overall response of ≥ VGPR based on investigator assessment. PFS was longer in arm Rd compared with that in arm MPT for this subgroup of subjects. The improvement in median PFS time between arm Rd (52.5 months) and arm MPT (31.8 months) was 20.7 months, with a 48% reduction in the risk of disease progression or death for subjects treated with Rd compared with those treated with MPT (HR 0.52; 95% CI: 0.40–0.66).

B.2.7.5 MM-020 OS analysis by subgroup

OS subgroup analysis was also generally consistent with the overall ITT population, except for the smaller subgroups of patients with severe renal function insufficiency (HR 1.20, 95% CI 0.76–1.92).[43] HR by subgroup for the comparison of OS between arm Rd vs arm MPT (ITT population) can be found in Appendix E, Figure 34.

OS based on response (Post Hoc analysis)

A secondary analysis was conducted to look at OS outcomes by depth of response. In patients who achieved ≥ VGPR the median OS for patients receiving Rd was 79.5 months compared with 55.7 months for patients receiving MPT (HR 0.63; 95% CI 0.48–0.83).

B.2.8 Meta-analysis

N/A

B.2.9 Indirect and mixed treatment comparisons

The evidence on PFS and OS identified by the SLR (Table 62) described in Appendix D was synthesised using NMA. A summary of the methodology and outcomes of the 4 studies used in the NMA is presented in Appendix D, Table 60. All studies were deemed high quality using a Cochrane risk of bias analysis, Appendix D, Table 67. A description of the NMA methods is also provided in Appendix D.

B.2.9.1 Overview of the NMA

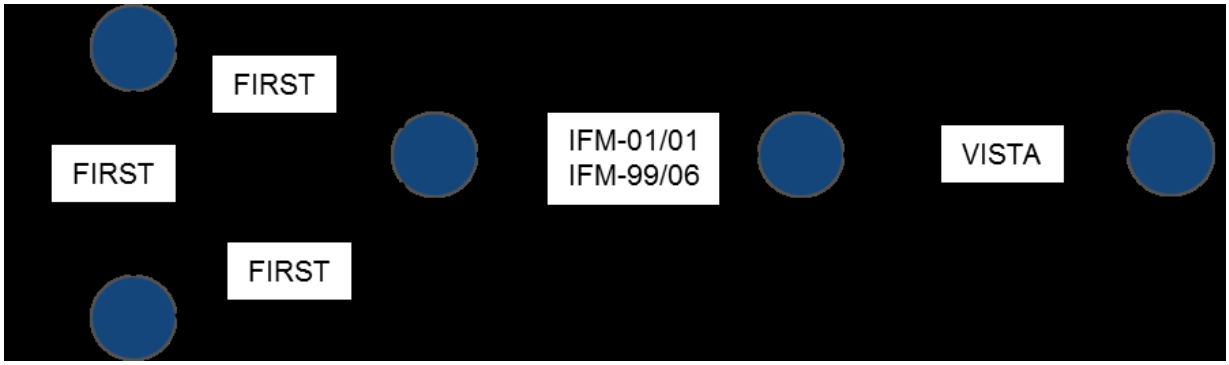
The trials included in the NMA are summarised in Table 17 and the network is shown in Figure 14. As described in Appendix D, of the 23 studies identified by the search and full text screening, only the following 4 trials which provided direct or indirect evidence on comparisons of licensed doses of Rd, MPT, or VMP were included in the NMA; FIRST/MM-020, IFM-01/011, IFM-99/06, and VISTA. MP was included within the network to allow connection of VMP to the network via the VISTA trial.

Table 17 Summary of the trials used to carry out the NMA

Study	MP	MPT	VMP	Rd
IFM-99/06 (Facon[38])	Yes	Yes		
IFM 01/01 (Hulin[69])	Yes	Yes		
VISTA (San Miguel; Mateos[39,40,70])	Yes		Yes	
FIRST/MM-020 (Benboubker[31])[a]		Yes		Yes

[a] PFS and OS data taken from MM-020 CSR[43] and data on file,[68] both 21 January 2016 data cut off.
Key: MP, melphalan and prednisone; **MPT**, melphalan, prednisone, and thalidomide; **NMA**, network meta-analysis; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, 18 cycles of lenalidomide and dexamethasone; **VMP**, bortezomib, melphalan, and prednisone.

Figure 14 Network of trials included in the analysis



Key: MP, melphalan and prednisone; **MPT**, melphalan, prednisone, and thalidomide; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, 18 cycles of lenalidomide and dexamethasone; **VMP**, bortezomib, melphalan, and prednisone.

B.2.9.2 Results of the analysis

NMAs were conducted using both constant HR (i.e. assuming proportional hazards) and time-varying HR models, since it was not known in advance which would provide the best combination of fit and parsimony.

The constant HRs NMA should be considered the primary analysis for both PFS and OS as the time-varying HRs NMA results did not indicate a statistically significant time-dependency in the HRs for either endpoint. Specifically, the 95% credible intervals [CrI] for the d1 parameter, which reflects the change in the ln(HR) over time, include 0 for both for all comparisons for PFS (Table 20) and OS (Table 18). In other words, the change in ln(HR) over time was not statistically different from 0 for any comparison, hence it is reasonable to assume proportional hazards and therefore use the outputs of the constant HR NMA for PFS and OS.

Overall survival – constant HRs

The results indicate that Rd was associated with a lower risk of death compared with MP (HR 0.49, 95% CrI 0.37–0.64), MPT (HR 0.78, 95% CrI 0.67–0.91) and VMP (HR 0.70, 95% CrI 0.50–0.98). These results were statistically significant (Table 18).

Table 18 Results of fixed effects constant HRs NMA of OS

MP	**1.60 (1.28, 1.99)**	**2.05 (1.56, 2.68)**	**2.08 (1.59, 2.71)**	**1.44 (1.17, 1.76)**
0.63 (0.50, 0.78)	**MPT**	**1.28 (1.10, 1.50)**	**1.30 (1.11, 1.52)**	0.90 (0.67, 1.21)

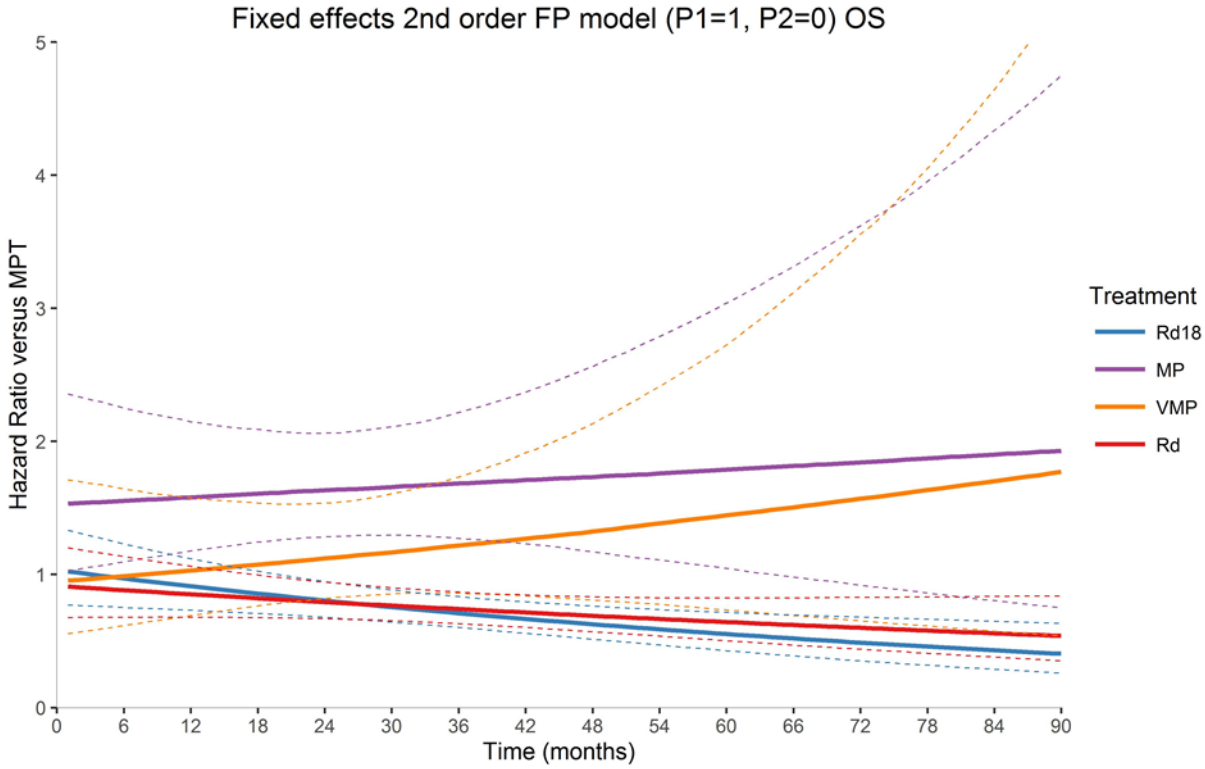
0.49 (0.37, 0.64)	**0.78 (0.67, 0.91)**	**Rd**	1.01 (0.87, 1.18)	**0.70 (0.50, 0.98)**
0.48 (0.37, 0.63)	**0.77 (0.66, 0.90)**	0.99 (0.84, 1.15)	**Rd18**	**0.69 (0.49, 0.97)**
0.70 (0.57, 0.85)	1.11 (0.82, 1.50)	**1.42 (1.02, 2.00)**	**1.44 (1.03, 2.02)**	**VMP**

Fixed effects NMA. Data are presented as the HR (95% CrI). Values correspond to the HR between the row versus the column. Values in bold are statistically significant at the 0.05 significance level.
Key: CrI, credible interval; **HR**, hazard ratio; **MP**, melphalan and prednisone; **MPT**, melphalan, prednisone, and thalidomide; **NMA**, network meta-analysis; **OS**, overall survival; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, 18 cycles of lenalidomide and dexamethasone; **VMP**, bortezomib, melphalan, and prednisone.

Overall survival – time-varying HRs

Under the best fitting 2nd order fractional polynomial model (Appendix D, Table 64) the HR for Rd vs. MPT is lower than 1 from the beginning of treatment and this difference becomes statistically important at approximately 20 months. The hazard ratios over time are plotted in Figure 15 and the corresponding parameters are reported in Table 19.

Figure 15 Results of fixed-effects 2nd order fractional polynomial model NMA of OS; hazard ratios over time vs. MPT



Key: MP, melphalan and prednisone; **NMA**, network-meta analysis; **OS**, overall survival; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, 18 cycles of lenalidomide and dexamethasone; **VMP**, bortezomib, melphalan, and prednisone.

Table 19 Basic parameter estimates of 2nd order FP model (p1=1, p2=0); OS

Treatment	d0 estimate	d0 variance	d0 CrI	d1 estimate	d1 variance	d1 CrI	correlation
MPT	Reference						
Rd18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

d0 is the treatment effect with constant HR; d1 reflects the change in the log(HR) over time.[71]

Progression-free survival – constant HRs (with EMA-censored MM-020 data)

Rd demonstrated the lowest risk of disease progression or death compared with MP (HR 0.41, 95% CrI 0.33–0.52), MPT (HR 0.74; 95% CrI 0.65–0.85) and VMP (HR 0.74; 95% CrI 0.52–1.05). The comparisons of Rd with MP and MPT were statistically significant (Table 20).

Table 20 Results of fixed effects constant HRs NMA of PFS (with EMA-censored MM-020 data)

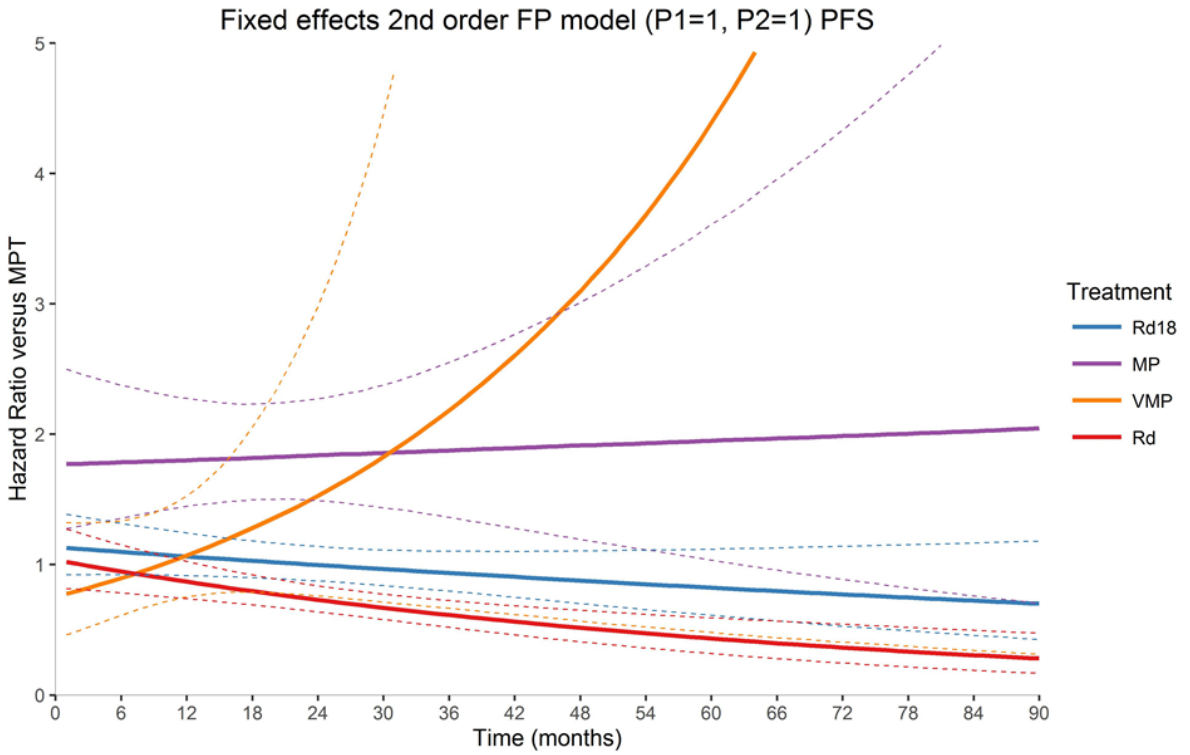
MP	**1.79 (1.47, 2.17)**	**2.42 (1.91, 3.06)**	**1.74 (1.37, 2.19)**	**1.79 (1.39, 2.32)**
0.56 (0.46, 0.68)	**MPT**	**1.35 (1.18, 1.54)**	0.97 (0.85, 1.11)	1.00 (0.73, 1.38)
0.41 (0.33, 0.52)	**0.74 (0.65, 0.85)**	**Rd**	**0.72 (0.63, 0.82)**	0.74 (0.52, 1.05)
0.58 (0.46, 0.73)	1.03 (0.90, 1.18)	**1.39 (1.22, 1.59)**	**Rd18**	1.03 (0.73, 1.46)
0.56 (0.43, 0.72)	1.00 (0.72, 1.38)	1.35 (0.95, 1.92)	0.97 (0.68, 1.37)	**VMP**

Fixed effects NMA. Data are presented as the HR (95% CrI). Values correspond to the HR between the row versus the column. Values in bold are statistically significant at the 0.05 significance level.
Key: CrI, credible interval; **EMA,** European Medicines Agency; **HR**, hazard ratio; **MP**, melphalan and prednisone; **MPT**, melphalan, prednisone, and thalidomide; **NMA**, network meta-analysis; **PFS**, progression-free survival; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, 18 cycles of lenalidomide and dexamethasone; **VMP**, bortezomib, melphalan, and prednisone.

Progression-free survival – time-varying HRs (with EMA-censored MM-020 data)

Under the best-fitting 2nd order fractional polynomial model (Appendix D, Table 65), the HR of Rd relative to MPT decreases over the course of follow-up, with the difference becoming statistically important at approximately 18 months. The hazard ratios over time are plotted in Figure 16 and the corresponding parameters are reported in Table 21. The credible intervals for the HR of VMP relative to MPT are wide, indicating substantial uncertainty particularly after 24 months.

Figure 16 Results of fixed-effects 2nd order fractional polynomial model NMA of PFS with EMA-censored MM-020 data; hazard ratios over time vs. MPT



Key: MP, melphalan and prednisone; **MPT**, melphalan, prednisone, and thalidomide; **NMA,** network-meta analysis; **PFS**, progression-free survival; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18,** 18 cycles of lenalidomide and dexamethasone; **VMP**, bortezomib, melphalan, and prednisone

Table 21 Basic parameter of 2nd order FP model (p1=1, p2=1); PFS with EMA-censored MM-020 data

Treatment	d0 estimate	d0 variance	d0 CrI	d1 estimate	d1 variance	d1 CrI	correlation
MPT	Reference						
Rd18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Rd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

d0 is the treatment effect with constant HR; d1 reflects the change in the log(HR) over time.[71]

B.2.10 Adverse reactions

B.2.10.1 Safety evidence from MM-020

Safety data reported are from the MM-020 study CSR to a data cut-off of 21 January 2016.[43] Data for all 1,613 patients who received at least one dose of any study drug were included.[43] Safety outcomes assessed in the MM-020 study included evaluation of AEs, vital signs, neurological examination, clinical laboratory evaluations (including haematological), electrocardiogram (ECG), pregnancy testing and pregnancy prevention risk management, and incidence of second primary malignancy (SPM).

B.2.10.2 Adverse reactions reported in MM-020

Extent of exposure to study treatment: treatment duration and intensity

The treatment duration and cumulative exposure to treatments, per treatment group within the safety population, are summarised in Table 69, Appendix F.[43] The median treatment duration in the Rd group was 80.2 weeks (range, 0.7–374.1) compared with 72 weeks in the Rd18 group (range, 0.9–102.6) or 67.1 weeks in the MPT group (range, 0.1–110.0). The difference in treatment duration can mainly be attributed to study design, which proposed that the Rd arm be continued until disease progression.[43]

As of the 21 January 2016, 208 patients in the Rd group (39%) were treated for > 2 years; 138 patients (26%) were treated for > 3 years; 96 patients (18%) were treated for > 4 years; 72 patients (13.5%) were treated for > 5 years and 30 patients (6%) were treated for > 6 years. The median number of cycles on study treatment was 19.0 cycles (range, 1–92 cycles) in the Rd group, 18.0 cycles in Rd18 group (maximum number of cycles allowed per protocol) and 10.0 cycles in the MPT group (below the maximum 12 cycles allowed per protocol). The total number of person-years on study treatment in each treatment arm was 1130 in the Rd group, 587 in the Rd18 group and 549 in the MPT group.

For patients receiving Rd and Rd18, the median relative dose intensities (RDIs) for lenalidomide and dexamethasone were [redacted] and [redacted], respectively. In the MPT arm, the median RDIs for melphalan, prednisone and thalidomide were 0.9, 1.0 and 0.8, respectively. More patients receiving Rd18 completed lenalidomide treatment at the full planned dose as compared with patients receiving thalidomide or melphalan in the MPT arm. Most patients who continued lenalidomide plus low-dose dexamethasone beyond 18 cycles (i.e. in the Rd arm) did so with limited need for additional dose reductions of both study drugs.

Treatment-emergent adverse events

AEs were more likely to occur shortly after treatment initiation and decrease in frequency over time. Almost all patients (> 99%) in all three treatment arms had at least one treatment-emergent AE (TEAE) during active treatment (Table 22).[43]

The most frequently reported AEs across the study included constipation, neutropenia and anaemia, followed by peripheral oedema, diarrhoea, fatigue, nausea, back pain, asthenia, peripheral sensory neuropathy, thrombocytopenia, rash, insomnia and dyspnoea. Constipation, nausea, peripheral sensory neuropathy and neutropenia were reported more frequently in the MPT group than in patients receiving Rd or Rd18. While less frequent, the AEs of muscle spasm, pneumonia, decreased appetite, hyperglycaemia and weight decreased were reported more frequently (with a between-group difference of ≥ 5%) for Rd18 compared with MPT, and the AEs of peripheral oedema, paraesthesia, dizziness, vomiting, tremor, peripheral neuropathy, thrombocytopenia, leukopenia and lymphopenia were reported more frequently in the MPT group than in the Rd18 group.[43]

AEs were generally reported at a higher frequency for Rd than Rd18, possibly reflecting its longer treatment duration. Cataract, which is a well-known toxicity associated with prolonged glucocorticoid administration,[72] was reported in more than twice as many patients receiving continuous Rd. Cataract has been observed with lenalidomide in combination with dexamethasone for a prolonged period of time and this potential AE is described in the lenalidomide (REVLIMID®) SmPC.[5]

Grade 3–4 treatment-emergent adverse events

In patients receiving MPT, 88.7% had at least one grade 3–4 TEAE compared with 80.2% in patients receiving Rd18, despite the similar 72-week, protocol-specified treatment duration (Table 22). In patients receiving Rd, 86.3% reported a grade 3–4 TEAE.[43] Blood and lymphatic system disorder AEs, including neutropenia, anaemia, thrombocytopenia, leukopenia, lymphopenia and febrile neutropenia, were the most frequently reported grade 3–4 AEs in each treatment group. Grade 3–4 neutropenia was notably more frequent in patients receiving MPT (44.9%) than with Rd18 (26.5%) and Rd (29.5%). Grade 3–4 thrombocytopenia and leukopenia were also more frequent in the MPT group occurring at rates at least 2% higher than those observed in patients receiving Rd and Rd18.

In addition, grade 3–4 nervous system disorder AEs such as peripheral sensory neuropathy were also notably more frequent in patients receiving MPT (Rd [1.1%], Rd18 [0.4%] and MPT [9.4%]). Grade 3–4 infections and infestations TEAE were reported in 31.6% of patients treated with Rd and in 21.9% and 17.2% of patients in the Rd18 and MPT groups, respectively.

The incidence of grade 3–4 TEAEs was also stratified according to age: ≤ 75 years and > 75 years. Fewer grade 3 or 4 TEAEs were reported in patients aged ≤ 75 years receiving Rd or Rd18 than in those receiving MPT (84.7% with Rd, 77.3% with Rd18, 89.4% with MPT).[43] For patients > 75 years of age, TEAE rates were similar among treatment groups (89.2% with Rd, 85.4% with Rd18, 87.5% with MPT). The pattern and types of TEAE reported in each of the two age groups was similar to that reported in the overall ITT population.[73] Through dose adjustments and monitoring, Rd can be an effective and tolerable option even in elderly and frail patients.

Serious treatment-emergent adverse events

All treatment-emergent SAEs that were reported in ≥ 1% of patients in any treatment arm are summarised in Appendix F, Table 70.

The frequency of all treatment-emergent SAEs was higher for patients receiving Rd (71.1%) and Rd18 (57.0%) than with MPT (49.9%).[43] Few individual SAEs occurred at a rate of ≥ 2% in any treatment arm. The most frequently reported SAEs in the

study in all arms were infections and infestations affecting 24.4%, and these were often respiratory infections. The most frequently occurring SAE was pneumonia, which was reported in 11.1% patients receiving Rd, 8.9% patients receiving Rd18 and 6.5% patients receiving MPT.

In terms of treatment-emergent SAEs related to any study drug, these were similar for patients receiving the MPT and Rd18 regimens, but were more frequent in the group receiving Rd, reflecting the longer drug-exposure time in this arm. Most drug-related SAEs in each arm were reported with frequencies of 3% or less, except for pneumonia (Rd 5.8%, Rd18 4.3% and MPT 3.0%); pulmonary embolism (Rd 3.8%, Rd18 2.8% and MPT 3.1%) and deep vein thrombosis (Rd 3.4%, Rd18 1.9% and MPT 1.5%).[43]

Table 22 TEAEs that occurred in ≥ 10% of patients of any grade in either treatment group by system organ class and preferred term (safety population) and corresponding Grade 3/4 TEAEs in the MM-020 study

	Rd, n (%) (n = 532)		Rd18, n (%) (n = 540)		MPT, n (%) (n = 541)	
System Organ Class	**All grade AEs**	**Grade 3/4**	**All grade AEs**	**Grade 3/4**	**All grade AEs**	**Grade 3/4**
Patients with ≥ 1 AE	**529 (99.4)**	**459 (86.3)**	**536 (99.3)**	**433 (80.2)**	**539 (99.6)**	**480 (88.7)**
General Disorders and Administration Site Conditions	**446 (83.8)**	**139 (26.1)**	**430 (79.6)**	**126 (23.3)**	**423 (78.2)**	**106 (19.6)**
Oedema (peripheral)	219 (41.2)	18 (3.4)	169 (31.3)	10 (1.9)	215 (39.7)	16 (3.0)
Fatigue	180 (33.8)	42 (7.9)	177 (32.8)	46 (8.5)	154 (28.5)	31 (5.7)
Asthenia	155 (29.1)	45 (8.5)	123 (22.8)	33 (6.1)	125 (23.1)	32 (5.9)
Pyrexia	125 (23.5)	17 (3.2)	102 (18.9)	7 (1.3)	76 (14.0)	7 (1.3)
Gastrointestinal Disorders	**437 (82.1)**	**82 (15.4)**	**411 (76.1)**	**58 (10.7)**	**412 (76.2)**	**67 (12.4)**
Diarrhoea	251 (47.2)	25 (4.7)	208 (38.5)	18 (3.3)	89 (16.5)	8 (1.5)
Constipation	235 (44.2)	12 (2.3)	212 (39.3)	10 (1.9)	285 (52.7)	29 (5.4)
Nausea	157 (29.5)	5 (0.9)	128 (23.7)	4 (0.7)	165 (30.5)	13 (2.4)
Vomiting	102 (19.2)	4 (0.8)	68 (12.6)	2 (0.4)	109 (20.1)	10 (1.8)
Abdominal pain	73 (13.7)	8 (1.5)	41 (7.6)	6 (1.1)	30 (5.5)	3 (0.6)
Dyspepsia	59 (11.1)	2 (0.4)	28 (5.2)	1 (0.2)	36 (6.7)	0 (0.0)
Dry mouth	38 (7.1)	0 (0.0)	38 (7.0)	0 (0.0)	62 (11.5)	1 (0.2)
Musculoskeletal and Connective Tissue Disorders	**414 (77.8)**	**108 (20.3)**	**367 (68.0)**	**91 (16.9)**	**312 (57.7)**	**77 (14.2)**
Back pain	181 (34.0)	39 (7.3)	145 (26.9)	34 (6.3)	116 (21.4)	28 (5.2)
Muscle spasms	115 (21.6)	3 (0.6)	102 (18.9)	3 (0.6)	61 (11.3)	4 (0.7)
Arthralgia	111 (20.9)	9 (1.7)	71 (13.1)	8 (1.5)	67 (12.4)	8 (1.5)
Bone pain	91 (17.1)	17 (3.2)	77 (14.3)	15 (2.8)	62 (11.5)	14 (2.6)
Pain in extremity	91 (17.1)	9 (1.7)	66 (12.2)	8 (1.5)	61 (11.3)	7 (1.3)

Musculoskeletal pain	72 (13.5)	3 (0.6)	59 (10.9)	5 (0.9)	36 (6.7)	2 (0.4)
Musculoskeletal chest pain	64 (12.0)	6 (1.1)	51 (9.4)	5 (0.9)	39 (7.2)	3 (0.6)
Infections and Infestations	**402 (75.6)**	**168 (31.6)**	**377 (69.8)**	**118 (21.9)**	**305 (56.4)**	**93 (17.2)**
Bronchitis	97 (18.2)	10 (1.9)	59 (10.9)	6 (1.1)	43 (7.9)	3 (0.6)
Nasopharyngitis	90 (16.9)	1 (0.2)	54 (10.0)	0 (0.0)	33 (6.1)	0 (0.0)
Urinary tract infection	80 (15.0)	9 (1.7)	63 (11.7)	8 (1.5)	41 (7.6)	3 (0.6)
Pneumonia	76 (14.3)	49 (9.2)	68 (12.6)	45 (8.3)	40 (7.4)	31 (5.7)
Upper respiratory tract infection	74 (13.9)	4 (0.8)	53 (9.8)	8 (1.5)	31 (5.7)	3 (0.6)
Nervous System Disorders	**378 (71.1)**	**95 (17.9)**	**333 (61.7)**	**58 (10.7)**	**429 (79.3)**	**164 (30.3)**
Peripheral sensory neuropathy	113 (21.2)	6 (1.1)	93 (17.2)	2 (0.4)	191 (35.3)	51 (9.4)
Dizziness	89 (16.7)	4 (0.8)	70 (13.0)	4 (0.7)	115 (21.3)	16 (3.0)
Paraesthesia	88 (16.5)	0 (0.0)	74 (13.7)	0 (0.0)	103 (19.0)	14 (2.6)
Headache	81 (15.2)	3 (0.6)	52 (9.6)	2 (0.4)	56 (10.4)	5 (0.9)
Tremor	76 (14.3)	5 (0.9)	73 (13.5)	4 (0.7)	100 (18.5)	9 (1.7)
Neuropathy peripheral	35 (6.6)	12 (2.3)	22 (4.1)	5 (0.9)	62 (11.5)	21 (3.9)
Blood and Lymphatic System Disorders	**355 (66.7)**	**235 (44.2)**	**325 (60.2)**	**214 (39.6)**	**423 (78.2)**	**315 (58.2)**
Anaemia	243 (45.7)	100 (18.8)	193 (35.7)	85 (15.7)	229 (42.3)	102 (18.9)
Neutropenia	195 (36.7)	157 (29.5)	178 (33.0)	143 (26.5)	328 (60.6)	243 (44.9)
Thrombocytopenia	111 (20.9)	48 (9.0)	100 (18.5)	43 (8.0)	135 (25.0)	60 (11.1)
Leukopenia	66 (12.4)	25 (4.7)	60 (11.1)	30 (5.6)	94 (17.4)	53 (9.8)
Lymphopenia	60 (11.3)	31 (5.8)	43 (8.0)	18 (3.3)	71 (13.1)	37 (6.8)
Respiratory, Thoracic and Mediastinal Disorders	**314 (59.0)**	**90 (16.9)**	**259 (48.0)**	**53 (9.8)**	**246 (45.5)**	**54 (10.0)**
Cough	129 (24.2)	4 (0.8)	94 (17.4)	1 (0.2)	68 (12.6)	3 (0.6)
Dyspnoea	121 (22.7)	32 (6.0)	89 (16.5)	22 (4.1)	113 (20.9)	18 (3.3)
Metabolism and Nutrition Disorders	**309 (58.1)**	**131 (24.6)**	**274 (50.7)**	**87 (16.1)**	**192 (35.5)**	**62 (11.5)**
Decreased appetite	131 (24.6)	16 (3.0)	115 (21.3)	7 (1.3)	72 (13.3)	5 (0.9)

Hypokalaemia	106 (19.9)	45 (8.5)	62 (11.5)	20 (3.7)	38 (7.0)	11 (2.0)
Hyperglycaemia	64 (12.0)	28 (5.3)	52 (9.6)	23 (4.3)	19 (3.5)	9 (1.7)
Hypocalcaemia	62 (11.7)	25 (4.7)	56 (10.4)	19 (3.5)	31 (5.7)	8 (1.5)
Skin and Subcutaneous Tissue Disorders	**298 (56.0)**	**53 (10.0)**	**276 (51.1)**	**47 (8.7)**	**217 (40.1)**	**38 (7.0)**
Rash	120 (22.6)	33 (6.2)	131 (24.3)	28 (5.2)	93 (17.2)	28 (5.2)
Psychiatric Disorders	**264 (49.6)**	**39 (7.3)**	**234 (43.3)**	**34 (6.3)**	**167 (30.9)**	**14 (2.6)**
Insomnia	150 (28.2)	4 (0.8)	127 (23.5)	6 (1.1)	53 (9.8)	0 (0.0)
Depression	67 (12.6)	10 (1.9)	46 (8.5)	4 (0.7)	30 (5.5)	1 (0.2)
Vascular Disorders	199 (37.4)	58 (10.9)	148 (27.4)	35 (6.5)	138 (25.5)	35 (6.5)
Deep vein thrombosis	55 (10.7)	29 (5.5)	36 (6.7)	20 (3.7)	20 (3.7)	14 (2.6)
Hypotension	57 (10.7)	11 (2.1)	35 (6.5)	8 (1.5)	36 (6.7)	6 (1.1)
Eye Disorders	**183 (34.4)**	**51 (9.6)**	**126 (23.3)**	**22 (4.1)**	**86 (15.9)**	**7 (1.3)**
Cataracts	87 (16.4)	37 (7.0)	31 (5.7)	14 (2.6)	5 (0.9)	3 (0.6)
Investigations	**182 (34.2)**	**55 (10.3)**	**173 (32.0)**	**36 (6.7)**	**142 (26.2)**	**30 (5.5)**
Weight decreased	74 (13.9)	11 (2.1)	78 (14.4)	4 (0.7)	48 (8.9)	4 (0.7)

Data cut-off date = 21 January 2016.

The safety population: defined as all the patients who underwent randomisation and received at least one dose of the study treatments (lenalidomide, dexamethasone, melphalan, prednisone or thalidomide). System Organ Classes and Preferred Terms are coded using MedDRA version 15.1.

System Organ Classes and Preferred Terms listed in descending order of frequency for the Rd group.

Key: AE, adverse event; **MPT**, melphalan, prednisone and thalidomide; **Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone given for 18 cycles; **TEAE**, treatment-emergent adverse event.

Source: Clinical Study Report CC-5013-MM-020/IFM 07-01[43] and safety table 14.3.1.2.4.1.[68]

Other events of interest: second primary malignancies

In MM-020 at the data cut-off of 21 January 2016, the median follow-up time for surviving patients in the safety population was 67.1 months (range, 0.1–86.8 months).[43] A total of 192 (11.9%) of the 1,613 patients in all three treatment groups experienced at least one SPM. Overall, the proportion of patients with SPMs were similar for all three treatment groups (Rd [11.5%], Rd18 [11.1%] and MPT [13.1%]; see Appendix F, Table 71). The proportion of patients with invasive haematological and solid tumour SPMs were similar for the Rd and Rd18 groups (6.8% and 7.0%, respectively). A higher frequency of invasive SPMs was observed in the MPT group (8.5%). Of the patients (n = 20) with invasive haematological SPMs, 3 patients were in the Rd group, 2 in the Rd18 group and 14 were in the MPT group.

In a separate meta-analysis of pooled data from 3,254 patients with NDMM, it was shown that the increased risk of developing haematological SPMs was mainly driven by coexposure to the use of IMiDs and melphalan.[74] It is also worth noting that in the meta-analysis, the incidence of death due to myeloma or treatment-associated AEs were substantially higher than those due to SPMs[74] an observation reflected in study MM-020[43] and recognised in a recently published consensus paper by the IMWG.[75]

Death

At the 21 January 2016 data cut-off, a lower proportion of patients receiving Rd had died (53.4%, [284/532]) when compared with patients receiving MPT (62.1% [336/541]). In the Rd18 treatment group the overall percentage of deaths was similar to that for patients receiving Rd (52.4%, [283/540]). The most common cause of death in these treatment groups was MM (19.9%, 23.5%, and 27.5%, for Rd, Rd18 and MPT respectively). Other common causes of death were Infections accounting for 9.2%, 5.7%, and 8.5% of deaths, respectively, and death attributable to cardiac disorders in 5.8%, 5.2% and 3.7%, respectively.[43]

Treatment discontinuations, dose reductions and dose interruptions

Most treatment discontinuations in MM-020 were due to disease progression 50.7% [271/535] in patients receiving Rd, compared with 66.9% [362/541] and 61.6% [337/547] in patients receiving Rd18 and MPT, respectively. Few patients

discontinued treatment because of AEs; the discontinuation rates were 12.0%, 13.1% and 13.9% in patients receiving Rd, Rd18 and MPT, respectively.[43]

Across all treatment groups, dose interruptions were more common than dose reductions. TEAEs leading to dose interruption of thalidomide occurred for 71.9% of patients receiving MPT compared with an interruption of lenalidomide in 68.0% and 55.7% of patients receiving Rd and Rd18, respectively. Dose reductions of thalidomide occurred for 47.0% of patients receiving MPT compared with a reduction of lenalidomide in 41.4 and 28.7% of patients receiving Rd and Rd18, respectively.

In some patients, TEAEs led to lenalidomide or thalidomide discontinuation. Thalidomide was discontinued in 27.0% of patients receiving MPT compared with lenalidomide discontinuation in 25.6% and 17.2% of patients receiving Rd and Rd18, respectively. AEs in the nervous system disorders system organ class (SoC) led to discontinuations of thalidomide in 12.6% of patients receiving MPT compared with 3.6% and 1.9% discontinuations of lenalidomide in the Rd and Rd18 treatment groups, respectively. No specific, individual AEs led to discontinuation of any study drug in more than 2% of patients in any treatment arm, except for peripheral sensory neuropathy leading to discontinuation of thalidomide in 6.7% of patients receiving MPT.

Additional safety issues

Potential teratogenic risk, may be important to consider with regard to use of lenalidomide combinations in patients with transplant-ineligible NDMM, as described in the lenalidomide SmPC 'Special warning and precautions for use'.[5]

B.2.10.3 Safety summary for lenalidomide in transplant-ineligible NDMM

Safety analyses of MM-020 indicate that the Rd treatment regimen is manageable and that the superior efficacy of Rd over MPT is not compromised by increased toxicity.[43] The safety profiles of MPT and Rd in MM-020 were consistent with the safety profiles of these regimens established by previous studies.[38,69,76] Importantly, extension of Rd treatment beyond 36 months resulted in only a limited increase in AEs compared with Rd18 or MPT regimens.[43]

Rd was associated with fewer haematologic and neurologic toxic events, a moderate increase in infections, and fewer second primary malignancies than MPT,[31,43] a

current first-line regimen for transplant-ineligible patients with NDMM in the UK.[3] In MM-020, the rate of discontinuation as a result of AEs was lower with Rd treatment than with MPT. In addition, extended treatment with Rd beyond 72 weeks was associated with only a small increase in infections and thromboembolic events compared with stopping treatment.[43] It appears that long-term AEs with Rd beyond 72 weeks, such as a two-fold increase in the incidence of cataracts, are at least partly driven by glucocorticoids. This is a common finding in elderly patients with myeloma, indicating the need to investigate alternative ways to deliver glucocorticoids.[72]

The toxicity profile of Rd in study MM-020 supports the principle that Rd is appropriate for use as a continuous treatment in patients with MM.[5] This approach is important to keep residual disease at bay for as long as possible,[26] maximise the duration of the first remission and prevent deterioration in the QoL of patients.[31,47] In the UK, the existing frontline treatment options of either thalidomide or bortezomib in combination with an alkylating agent and a corticosteroid are limited to fixed treatment durations of 12 or 9 cycles, respectively, not only by their respective licenses but also by their toxicity.[17,37,38,41,42,69]

B.2.11 Ongoing studies

In transplant-ineligible patients with NDMM, there are no ongoing company-sponsored studies from which new evidence will become available in the timeline specified.

B.2.12 Innovation

Lenalidomide represents a step-change in the management of transplant-ineligible NDMM, it has the following innovative characteristics, which are meaningful to both patients and the NHS:

- Compared with thalidomide and bortezomib, it has a different mechanism of action and toxicity profile, which allows for continuous use to suppress residual disease and extend the period of first remission.
- As an oral therapy, lenalidomide provides an alternative to IV and injectable therapies such as bortezomib, which have to be given in the hospital setting.

Impact of different mechanism of action and toxicity profile

As a synthetic derivative of thalidomide, lenalidomide was developed with the aim of improving efficacy and reducing toxicity. Lenalidomide is more potent than thalidomide with regard to its anti-proliferative activity, anti-inflammatory properties and ability to stimulate Th1 cytokines, T-cells and natural killer cells.[4] These differences in molecular structure and activity result in an improved efficacy and toxicity profile compared with thalidomide and allow continuous treatment with lenalidomide until disease progression.[31,43] This approach helps suppress residual disease, extending the period of first remission, which is particularly important for older transplant-ineligible patients who may not respond to rescue therapy at the time of first relapse or have the opportunity to receive multiple lines of treatment due to cumulative treatment toxicities or comorbidities.[31,32]

Lenalidomide can also be given in a two-drug combination that does not include melphalan and, as such, may be more tolerable to older frail patients. Melphalan is a cytotoxic drug associated with many undesirable effects, including myelosuppression and hair loss. Melphalan is not suitable for long-term treatment because of its toxicity profile, including leukaemogenic properties.[77] Melphalan is associated with haematological toxicity and increased risk of SPM when given alone,[78-80] or in combination with IMiD®s.[74]

Reduction in patient burden and NHS resource use

Lenalidomide is an oral therapy that provides an alternative treatment to IV and subcutaneous therapies. The combination of lenalidomide and low-dose dexamethasone can be self-administered by patients at home. This is expected to be more convenient, easier and less distressing for patients than use of either IV or injectable combinations (e.g. VMP), particularly for elderly and frail individuals as well as those who live far away from hospitals. This is highly relevant when considering continuous treatment. The use of an oral agent provides patients with a greater sense of control over their disease and less interruption of their daily (including work) lives compared to IV and SC treatments.[49 81]

B.2.13 Interpretation of clinical effectiveness and safety evidence

Current clinical practice in the UK for patients with transplant ineligible NDMM makes use of the thalidomide and bortezomib based regimens, as advised by NICE guidance TA228.[3] These regimens are licensed for fixed treatment durations of between 9 and 12 cycles owing to associated toxicity issues.[41,42] As MM is characterised by regression and remission, and ultimately treatment failure, indicating the presence of residual disease even in patients who initially show a complete clinical response to treatment,[26] continuous therapy is required to maintain suppression of surviving tumour cells and extend the period of first remission.[26,27,30]

Rd Efficacy

The efficacy of lenalidomide in transplant-ineligible NDMM has been demonstrated in study MM-020, one of the largest trials in this population to date, comparing continuous use of Rd to progression with a current standard of care (MPT).[31,43] Rd demonstrated a significant improvement in PFS compared with MPT: [43,68]

- Final PFS by IRAC review using FDA censoring rules at the 24 May 2013 data cut off showed a 28% reduction in the risk of disease progression or death with Rd compared with MPT given for 72 weeks (HR 0.72; 95% CI 0.61–0.85; p = 0.00006).
- Updated PFS by investigator using FDA censoring rules at the 21 January 2016 data cut off demonstrated consistent results (HR 0.69; 95% CI 0.59–0.79; $p < 0.00001$).
- When these PFS data were analysed using EMA censoring rules, the Rd advantage over both MPT and Rd18 was still evident.

Rd demonstrated a significant improvement in OS compared with MPT:[43]

- Risk of death reduced by 22% (HR 0.78; 95% CI 0.62–0.90; p = 0.002) with a 10.0-month improvement in median OS.

Rd delivered a significantly quicker TTR and higher ORR (≥ PR) compared with MPT.[43]

- In Rd patients who had a best response of ≥ VGPR (48.6%), the PFS and OS benefit of Rd over MPT was even more profound:

    - Median PFS of 52.5 months for the Rd group compared with 31.8 months for MPT (HR 0.52; 95% CI: 0.40–0.66)
    - Median OS of 79.5 months for the Rd group compared with 55.7 months for MPT (HR 0.63; 95% CI: 0.48–0.83).

Rd treatment led to a longer DOR, TTP, time to second AMT and PFS2 compared to MPT:[43,68]

- Rd demonstrated sustained disease control delaying the time to second-line AMT: Rd (36.7 months) compared with MPT (26.7 months; HR 0.63; 95% CI 0.54–0.73; $p < 0.00001$).

Finally, an indirect treatment comparison has demonstrated significantly longer OS and a PFS benefit with Rd compared with VMP (PFS, HR 0.74; 95% CrI 0.52–1.05; OS, HR 0.70; 95% CrI, 0.50–0.98).

Rd Safety

A continuous treatment approach requires agents that have acceptable toxicity profiles with limited detrimental impact on patients' QoL. Lenalidomide has a different safety profile to thalidomide and bortezomib that allows treatment until disease progression.[5] In study MM-020, the improved PFS with Rd is accompanied by an improvement in HRQoL,[47] lower rates of haematological AEs, haematological SPMs and peripheral sensory neuropathy compared with MPT. Most AEs associated with Rd tended to occur within the first 18 months of therapy and decreased over time. Continuing Rd beyond 18 months was associated with only a small increase in AEs compared with stopping treatment after 18 cycles.[43]

- Grade 3 or 4 AEs with Rd occurred slightly less frequently than with MPT (86.3% vs 88.7% of patients, respectively) despite the longer duration of treatment.[43] A moderate increase in infections, which can be an underlying feature of the disease, was observed in the Rd group; however, most cases of infection occurred in the absence of neutropenia.[43]
- Patients receiving MPT discontinued treatment sooner and more frequently prior to disease progression than patients receiving Rd. In addition, there were more AEs leading to treatment discontinuation in the MPT arm despite the shorter 72-week treatment duration.[43]

- Rd tolerability was good regardless of patient age, an important factor in the transplant-ineligible MM population which includes a high proportion of older patients.[43]
- In comparison with patients receiving thalidomide combinations, patients receiving Rd experience less peripheral neuropathy,[38,43,69,82] paraesthesia,[43] nausea,[43] dizziness,[43] constipation,[38,43,69] and neutropenia.[7] The UK MRC Myeloma IX study has shown that the toxicity associated with thalidomide combinations limits long-term treatment exposure. This led the authors to conclude that "use of agents with better tolerability profiles, such as lenalidomide may produce better results".[83]
- Worsening of neuropathy was rarely seen in trials of Rd[43,84] and rates of peripheral neuropathy were low compared to what is generally seen for thalidomide combinations.[38,42,82] In addition, as a two-drug combination that does not include melphalan, Rd may be more tolerable for older frail patients.
- Lenalidomide is structurally related to thalidomide, a known teratogen a pregnancy prevention programme (PPP) has been established to reduce the risk of foetal exposure.[5]

Rd quality of life

Multiple myeloma causes deterioration in HRQoL, which decreases as the burden of illness increases over time with progression of the disease.[85] Delaying disease progression and maintaining QoL is therefore an important treatment goal,[17] especially amongst older patients. In MM-020 the EORTC QLQ-C30 was used in addition to the EORTC QLQ-MY20 and EQ-5D, with results showing both statistically significant and clinically meaningful changes in HRQoL from baseline.[47]

- Relative to MPT, Rd demonstrated a significantly greater reduction in disease symptoms and side effects of treatment, and no evidence of inferiority to MPT in any of the pre-selected HRQoL domains. Rd also demonstrated consistent clinically meaningful improvement in utility on the EQ-5D.

These findings demonstrate that the improved PFS with Rd does not come at a cost of decreased HRQoL.[47]

B.2.13.1 Clinical effectiveness of Rd relative to current comparator treatments

In terms of efficacy, toxicity and HRQoL, Rd given until disease progression offers considerable benefit over MPT, which was deemed by clinical specialists who took part in the NICE TA228 assessment as equivalent to the unlicensed combination of CTD.[3] The NMA conducted as part of this submission also shows efficacy advantages of Rd given until disease progression over VMP.

Comparative toxicity and health related quality of life

All relevant comparators to lenalidomide, namely bortezomib and thalidomide-based regimens, are licensed for fixed treatment durations of between 9 and 12 cycles respectively due to associated toxicity.[41,42] In key studies of MPT patients reported an increased incidence of AEs, notably cytopenias, thrombosis, fatigue and peripheral neuropathy.[17] MPT can require numerous dose modifications because of cytopenia. Within the SLR, rates of grade 3–4 neutropenia ranged between 23 and 48%,[31,38,69] grade 3–4 thrombocytopenia between 3 and 14%[31,38] and grade 3–4 peripheral neuropathy between 2 and 9%.[31,38,69] In addition, between 13.9% and 45%[38,43,69] of patients discontinued because of a treatment-related AE (Appendix D).

In the VISTA study, VMP was associated with a significant worsening of QoL during the first 3–6 cycles of treatment and peripheral sensory neuropathy was reported more frequently than with MP.[39,46] In the VISTA study rates of grade 3–4 neutropenia, thrombocytopenia and peripheral neuropathy were 40, 38 and 13% respectively.[40,70] In addition, 15% of patients discontinued because of a treatment-related TEAE (see Appendix D).[70]

The safety profile of Rd is manageable and allows treatment until disease progression with a low rate of discontinuation due to AEs (12%), which was lower than MPT (13.9%) given for 72 weeks. It is also associated with low rates of grade 3–4 peripheral neuropathy (1%) and its efficacy does not come at the expense of QoL.[43,47]

Lenalidomide's improved safety profile means that patients who are unable to tolerate or who have contraindications to thalidomide may also benefit from Rd in addition to bortezomib combinations.[5,31,42,43] In practice, patients who present with

predisposing conditions that make them more susceptible to thalidomide AEs may benefit from receiving Rd.

Rd as an oral therapy

As an oral therapy, Rd can be self-administered by patients at home. In comparison, bortezomib based regimens, require patients to attend hospital (either in a day case or outpatient setting) to receive SC or IV administration twice weekly for the first four 28-day cycles followed by weekly administration thereafter.[41]

Clinical expert opinion

Through consultation with an Expert Advisory Panel of clinicians from England and Wales, It was highlighted that for older transplant-ineligible patients it is important to achieve a long first remission with treatment.[86] Clinical experts at the Advisory Panel highlighted:[86]

- MM-020 studied a patient cohort reflective of typical practice.[86] Specifically, the study included a large proportion of elderly patients and a reasonable percentage of patients with severe renal insufficiency.
- The case for continuous treatment with Rd is particularly strong in older patients, to achieve the longest PFS upfront. Rd through its oral formulation and toxicity profile enables the drug to be delivered continuously, unlike other agents such as bortezomib where the evidence is more limited.
- The OS data for Rd in MM-020 is impressive, particularly when compared with thalidomide-based and bortezomib-based regimens, and considering the age of patients in the trial.
- As an oral treatment Rd that may reduce pressure on day unit services.
- The toxicity profile of treatments in the older transplant-ineligible population is important and Rd is well tolerated.

This is further supported by a scoring exercise by the NCCN which scores Rd higher for safety (4 out of 5) than MPT and VMP (both 3 out of 5). It is also important to point out that the NCCN recommends Rd as a Category 1 option for treatment of patients with NDMM who are ineligible for transplantation.[61]

B.2.13.2 Strengths and limitations of the clinical evidence base

Strengths

The MM-020 study is one of the largest ever conducted in patients with transplant-ineligible NDMM (n = 1623). Baseline characteristics of the MM-020 study populations in all 3 treatment arms were well balanced in terms of median age, age distribution, ISS stage, performance status, cytogenetics and parameters of prognostic significance (e.g. baseline renal impairment).[43]

Efficacy was assessed using outcomes and time points that are consistent with previous regulatory submissions.[67] Primary and key secondary outcomes were assessed by IRAC review based on IMWG criteria an international standard for the assessment of response in MM studies.[62] To ensure an unbiased assessment of the data, the IRAC reviewed all efficacy data in a blinded manner (independent of investigator-reported response), and determined the response to therapy and time to progressive disease for each patient. Although the study was open-label the sponsor's study team was blinded to the study treatment code prior to the final analysis of PFS.[43]

The primary endpoint was PFS, which was significantly improved in patients receiving Rd therapy compared to MPT. PFS may be a purer measure of a drug's efficacy than OS because it eliminates potential differential bias from previous or subsequent treatments. PFS is increasing used as a primary outcome measure and the EMA have concluded that "in this setting, PFS is an acceptable primary endpoint".[87]

Results from pre-specified subgroup analyses suggest that the overall findings from study MM-020 would be transferable to the range of patients typically presenting at clinics in UK clinical practice, including older age groups. A PFS benefit in favour of Rd versus MPT was observed in most subgroups. When those subgroups defined as stratification factors (age, ISS stage, geographic region) were subject to statistical analysis, a significant PFS advantage for Rd over MPT was shown in all subgroups, except for those categories with relatively small patient numbers that likely suffered from a statistical under-powering.[43]

MM-020 also included a wide range of secondary outcomes highly relevant to MM including OS, myeloma response, DOR, TTR, TTF, time to second-line AMT and HRQoL. OS is still considered a gold standard in demonstrating clinical efficacy in oncology,[88] being an unambiguous endpoint that is relatively insensitive to investigator interpretation and directly reflects clinical benefit to patients. The positive impact of Rd therapy on OS (a 22% reduction in the risk of death relative to MPT)[43] is therefore an important finding that, coupled with the concomitant HRQoL benefit derived from an extended PFS,[43,47] adds to the significant weight of evidence.

PFS2 was an exploratory endpoint used to assess whether first-line treatment introduces treatment resistance disease in the subsequent line of therapy. The EMA has acknowledged the value of this alternative endpoint when maintenance regimens are under assessment.[67] PFS2 for Rd was significantly superior compared with MPT, supporting the long-term benefit from an extended first PFS with Rd treatment. The median PFS2 data for Rd help to rule out possible negative effects of this treatment on the next line of therapy.

HRQoL was included as an endpoint to measure the impact of the disease and of treatment on patients' QoL. This is an important outcome for patients, especially elderly patients[86] and was measured using validated oncology-specific and MM-specific questionnaires. The results show that the improved PFS with Rd is accompanied by an improvement in HRQoL.[47]

Finally, the MM-020 dataset is also now mature and all primary and secondary endpoints have been met, with 52.1% of patients on the Rd arm having experienced a progression and 53.5% of patients having died. This data maturity allows greater certainty around the longer term outcomes of Rd treatment.

Limitations

MM-020 did not include VMP despite this regimen being used in the UK and Europe. VMP could not be included, as this regimen was first approved for use in June 2008, which was after the start of the MM-020 study.[43] Instead, in this submission, an indirect comparison was used to compare Rd with VMP, via NMA, which shows statistically significant OS for Rd over VMP. At the time when the MM-020 study was being designed, MPT was chosen as a comparator because it was, and still is, a

standard first-line treatment regimen for elderly patients with NDMM. CTDa was developed as an alternative regimen to MPT by UK investigators and studied in the UK Myeloma IX study which compared CTDa with MP.[17,82] Outside of the UK, CTDa is not widely used and as such was not considered an appropriate comparator for the study.

Some pre-specified subgroups of MM-020 included few patients

The patient numbers are low in some of the pre-specified subgroups and thus no conclusions can be drawn from the results.[43] For example, only 142 patients were in the high risk cytogenetics group (defined as 4;14, 14;16 and del17p) across the three arms of the study. Among patients with a non-adverse cytogenetic risk profile, the risk of disease progression or death was reduced by 35% in the Rd treatment group compared with MPT (HR 0.65; 95% CI 0.52–0.81); however, for those who did have an adverse cytogenetic risk profile, the risk was non-significantly reduced by 18% (HR 0.82; 95% CI 0.63–1.07).

B.2.13.3 Relevance of the evidence base to the decision problem

Evidence from MM-020 is highly relevant as it included the same population in which Rd would be used in clinical practice in the UK: transplant-ineligible NDMM. Of the 1,623 patients randomised, 72 patients were recruited from 16 centres in the UK, making results applicable to UK practice. The Expert Advisory Panel of clinicians from England and Wales, highlighted that MM-020 studied a patient cohort reflective of typical practice.[86] Specifically, the study included a large proportion of elderly patients and a reasonable percentage of patients with severe renal insufficiency. At baseline, 35% of patients were > 75 years old, 41.6% had ISS Stage III disease, 9.1% had severe renal insufficiency (CrCl < 30 mL/min), 71.2% had a history of bone disease, and 13.5% had received radiation for MM prior to treatment in the study.[43]

The results indicate that patients aged over 75 years tolerate Rd until disease progression.[43] There was no relevant difference in grade 3–4 toxicity between patients younger and older than 75 years of age.[43,73] On viewing these data, the Expert Advisory Panel noted that patients in this age group will often not receive any treatment because of concerns over toxicity.[86] Transplant-ineligible patients are a particularly heterogeneous clinical group that includes fit elderly patients as well as patients considered as unfit or frail.[89] Drug-related treatment complications are

prevalent among elderly or frail patients with MM and may lead to premature discontinuation from treatment or lower dose intensities.[19] Indeed, BSCH guidelines highlight that the aim of therapy in patients who are older and less fit is to achieve the maximum durable response to treatment with minimal treatment-related toxicity.[17]

For elderly, unfit or frail patients who are not eligible for high-dose therapy and stem cell transplant, the IMWG recommend that treatment be adapted and highlight that a two-drug combination can improve tolerance without jeopardising drug activity.[90] This view was supported by The Expert Advisory Panel, who highlighted that treatment toxicity can be a limiting factor for older transplant-ineligible patients with NDMM and that there may be advantages of giving some patients the two-drug combination Rd over a three-drug bortezomib or thalidomide combination. This is particularly important in patients over 75 years of age, where response to treatment and toxicity are of importance.[86]

The comparator included in MM-020 is relevant to the decision problem. MPT was chosen because: 1) there is good evidence supporting its efficacy over MP;[91] 2) it is the only licensed thalidomide combination in this patient population;[42] and 3) it is recommended by the ESMO Clinical Practice Guidelines for MM, and is a standard regimen for NDMM in Europe.[59,60] The efficacy and safety of MPT have been investigated in a series of large studies and meta-analysis and MPT has shown OS benefit over MP.[91] The EMA considered MPT as the standard of care in Europe and considered both MPT and Rd, as given in MM-020, as appropriate treatment regimens.[2] MM-020 is the first, large, phase 3 study to compare the efficacy and safety of Rd with a current SoC, MPT (rather than MP) given for a fixed number of cycles, in transplant-ineligible patients with NDMM.[43]

B.2.13.4 Factors influencing internal and external validity

Study MM-020 is considered to have high internal validity (see Table 66, Appendix D) with results that are relevant to clinical practice in the UK.

B.2.13.5 Life-expectancy

In the USA, patients diagnosed with MM at the Mayo Clinic between 2001 and 2005 had a median OS of 4.6 years, which was lower than for those diagnosed between 2006 and 2010 (OS 6.1 years, $p = 0.002$).[92]

According to Cancer Research UK, about 77% of all patients diagnosed with myeloma in England and Wales live for at least 1 year after diagnosis. About 47% live for at least 5 years and it is estimated that 32% of people will live for at least 10 years.[93] It is important to point out that these statistics include both younger transplant-eligible and older transplant-ineligible patient populations and that 5 year OS for the latter would be expected to be lower.[93]

Although Rd offers an extension to life compared with current NHS treatment options (MPT and VMP), Rd does not qualify as a 'life-extending treatment at the end of life', Table 23.

Table 23 End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	N/A; median survival in the comparator arm of 49.1 months	Section B.2.6.4
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Demonstrated in MM-020	Section B.2.6

Key: N/A, not applicable; **NHS**, National Health Service.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A summary of the studies identified by the SLR (Appendix G) is presented in Table 24. The relevance of each study that was extracted to the decision problem is summarised below:

- Picot 2011[94,95] is the assessment report on the clinical effectiveness and cost-effectiveness of bortezomib and thalidomide in combination regimens with an alkylating agent and a corticosteroid for the first-line treatment of multiple myeloma from TA228.

- Garrison 2013[96] is a cost-effectiveness analysis of initial treatment of multiple myeloma with VMP vs. MPT or lenalidomide plus MP with continuous lenalidomide maintenance treatment. The study adopts a US payer perspective, however was included because it provides relevant information on model structure. ICERs for pairwise compairsons of VMP in the south-east quadrant reported as “VMP cost-saving” were corrected in the extractions.

- Usmani 2016[97] investigates the cost-effectiveness of Rd vs. VMP in transplant-ineligible patients with NDMM. Although US based, this publication compares Rd and VMP and provides relevant information on model structure.

- Celgene 2009[98] is the company submission for thalidomide in TA228. Extractions were based on the associated summary reported by Picot 2011 given adequate data were provided in this publication. Results were extracted from the tabulated base-case results for the Celgene submission.

- Janssen-Cilag 2009[99] is the company submission for bortezomib in TA228. Extractions were based on the associated summary reported by Picot 2011 given adequate data were provided in this publication. Results were extracted from the tabulated base-case results for the Janssen–Cilag submission.

Table 24 Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	Treatment	Total QALYs	Total costs	ICER (per QALY gained)
Picot[94,95]	2011	Partitioned survival model	NDMM patients ineligible for ASCT and/or older than 65 years.	MP	2.42	£21,439	Referent
				CTDa	2.68	£29,983	£33,031 (vs. MP)
				VMP	3.62	£57,168	£28,937 (vs. CTDa)
				MPT	3.64	£32,598	Dominates VMP
Garrison[96]	2013	Markov model	Untreated transplant-ineligible MM patients with an average age of 70 years at treatment initiation	VMP	2.994	$119,102	-
				MP	2.049	$63,294	$59,076 (vs. MP)
				MPT	2.951	$142,452	VMP dominates
				MPR-R	2.428	$248,358	VMP dominates
Usmani[97]	2016	Partitioned survival model	Initial treatment for transplant-ineligible patients with NDMM and/or older than 65 years.	VMP	2.79	$245,819	Referent
				Rd	4.26	$324,795	$53,826
Celgene[98]	2009	Markov model	Multiple myeloma patients who are older than 65 years or are 'ineligible for high-dose chemotherapy'.	MP	2.43	£1,365	-
				MPT	3.28	£21,133	£23,381 (vs. MP)
				VMP	3.35	£42,616	£303,845 (vs. MPT)
Janssen-Cilag[99]	2009	Partitioned survival model	Previously untreated multiple myeloma patients who are not eligible for high-dose chemotherapy with stem cell transplantation (65 years or older) and unable to tolerate or has contraindications to thalidomide.	MP	2.86	£54,434	-
				CTDa	3.07	£56,668	£10,905 (vs. MP)
				MPT	3.41	£59,322	£7,724 (vs. CTDa)
				VMP	4.03	£66,676	£11,907 (vs. MPT)

Key: **ASCT,** autologous stem cell transplant; **CTDa**, attenuated cyclophosphamide, thalidomide and dexamethasone; **ICER,** incremental cost-effectiveness ratio; **MP**, melphalan, prednisone; **MPR-R**, melphalan, prednisone and lenalidomide followed by lenalidomide maintenance; **MM**, multiple myeloma; **MPT**, melphalan, prednisone and thalidomide; **NDMM,** newly diagnosed multiple myeloma; **Rd;** lenalidomide and low-dose dexamethasone until disease progression; **QALY**, quality-adjusted life year; **VMP,** bortezomib, melphalan, and prednisone.

B.3.2 Economic analysis

As no UK model was identified which included Rd, a de novo economic model was developed to evaluate the cost-effectiveness of Rd in transplant-ineligible patients with NDMM. A description of the model and key features of the analysis is presented in the subsequent sections.

B.3.2.1 Patient population

In line with marketing authorisation and final scope, the cost-effectiveness analysis evaluates Rd in transplant-ineligible NDMM patients, using data for the ITT population from MM-020. The patient baseline patient characteristics from MM-020 are presented in Table 12.

The final scope also identifies a subgroup of patients who are unable to tolerate, or have contraindications to thalidomide. The comparator for this subgroup is VMP. A comparison with VMP has also been provided by indirectly comparing the ITT populations of MM-020 and VISTA. None of the trials included in the evidence network required patients to be intolerant or have contraindications to thalidomide; however, based upon the advice of clinical experts and the differences in toxicity profile and mechanism of action between thalidomide and lenalidomide, it was concluded that patients who present with predisposing conditions that make them more susceptible to thalidomide AEs may benefit from receiving Rd (Section B.2.13 and B.1.3.3 provide further details on the difference in toxicity profile of lenalidomide and thalidomide). This population could include patients with bowel disease, neuropathy, sleep disorders or who are extremely frail. For elderly, unfit or frail patients who are transplant-inelgible, the IMWG recommend that treatment be adapted and highlight that a two-drug combination can improve tolerance without jeopordising drug activity.[90] As such, use of data from the ITT population of these trials was considered appropriate for the cost-effectiveness analysis in the subgroup of patients who are unable to tolerate, or have contraindications to thalidomide.

The whole licensed population is being submitted for. However, a cost-effectiveness case cannot be made against MPT due to thalidomide's low acquisition cost. Instead, we ask the Committee to consider the evaluation comparing Rd with VMP in the identified subgroup (people who are unable to tolerate, or have contraindications

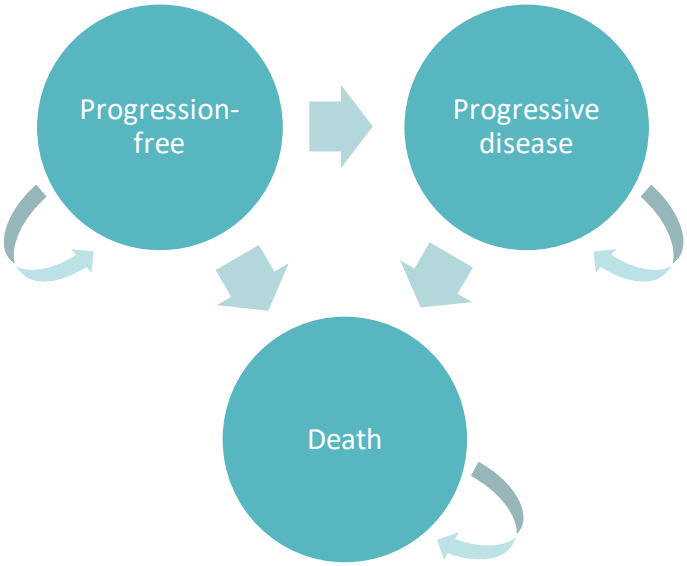
to thalidomide). VMP is recommended by NICE in TA228 for patients not eligible for transplant and who are unable to tolerate or have contraindications to thalidomide.[3]

B.3.2.2 Model structure

In line with recent NICE DSU guidance (TSD 19),[100] the following were considered when selecting the modelling approach: the structural link between health states, and associated issues identified in previous oncology appraisals[55] using parametric survival modelling (such as crossing of PFS and OS curves in deterministic and probabilistic sensitivity analysis [PSA]) and the availability of patient-level data from the key trials.[100]

A Markov model (Figure 17) was developed,[101] using multi-state modelling (MSM). The model included three health states: 'progression-free', 'progressive disease' and 'death' (Figure 17). All patients start in 'progression-free'; within each model cycle patients can then either remain 'progression-free', transit to 'progressive disease' (if they experience disease progression) or transit to 'death' (if they experience fatal progression). After entering 'progressive disease', within each model cycle patients either remain in this state or transit to 'death'. This structure captures the two key aspects of MM – survival and quality of life, which is impacted by disease progression and the effects of treatment being received.

Figure 17: Markov model structure



In this state-transition model, OS is a function of all individual transitions in the model, with the rate of death reflecting the evolving proportion of patients in the

progressed state and the differences in mortality between progression-free and progressed patients. Therefore, there is structural link between mortality and earlier progression events that is not captured when PFS and OS are modelled indepdently,[100] such as in partitioned survival models where the extrapolation of OS depends only on within-trial trends in mortality.

A multi-state Markov model describes how individuals move between a series of states in continuous time. For an individual in state r at time t, the next state (s) to which the individual moves and the time of the change are governed by a set of transition intensities: q_{rs}. Intensities, like hazards, represent the instantaneous risk of moving from state r to state s (e.g. q_{12} is the instantaneous risk of moving from 'progression-free' to 'progressive disease'). For the model structure defined in Figure 1, the transition intensity matrix $Q(t)$ is defined as:

$$Q(t) = \begin{bmatrix} q_{11} & q_{12} & q_{13} \\ 0 & q_{22} & q_{23} \\ 0 & 0 & 0 \end{bmatrix}$$

The primary output of the MSM analysis is a transition probability matrix: $P(t)$, the p_{rs} element of which denotes the probability of moving from state r to state s in each cycle.

$$P(t) = \begin{bmatrix} p_{11} & p_{12} & p_{13} \\ 0 & p_{22} & p_{23} \\ 0 & 0 & 1 \end{bmatrix}$$

For example, p_{12} is the probability of moving from 'progression-free' to 'progressive disease'. To calculate the estimated number of patients in each state in each cycle, the probability transition matrices are multiplied out. For example, if the number of patients at the previous cycle in 'progression-free', 'progressive disease' and 'death' was x, y and z, respectively, the model would estimate state occupancy in the current cycle as follows:

- Progression-free = $(p_{11} * x)$
- Progressive disease = $(p_{12} * x) + (p_{22} * y)$
- Death = $(p_{13} * x) + (p_{23} * y) + (1 * z)$

PFS and OS curves were produced by calculating the following:

- PFS; 'progression-free' state occupancy at each time-point.
- OS; sum of 'progression-free' and 'progressive disease' state occupancy

Health effects are calculated as both life years (LYs) and quality-adjusted life years (QALYs). Costs and health effects are accrued based on the proportion of patients in

the ‘progression-free’ and ‘progressive disease’ states over a 25-year time horizon, which is equivalent to lifetime given the starting age of patients in MM-020 (65 years) (Table 25). Model cycle length was 28 days, and half-cycle correction was applied.

Table 25 Features of the economic analysis

Factor	Previous appraisals	Current appraisal	
	TA228	Chosen values	Justification
Time horizon	Lifetime (30 years)	Lifetime (25 years). 15 and 35 years are explored as scenario analyses.	Sufficiently long to be considered a lifetime horizon based on a patient starting age of 65 years. >1% of patients alive across all arms at 25 years, 0% alive at 28 years
Discount rates	3.5% for costs and health effects	3.5% for costs and health effects	Consistency with the reference case
Source of effectiveness data	VISTA for VMP, IFM 99/06 and IFM 01/01 for MPT: OS and PFS survival curves, and HRs generated using weighted average survival at 6-month intervals	Rd and MPT use MM-020 trial. Comparative effectiveness for VMP from NMA including MM-020, VISTA, IFM-01/01 and IFM-99/06	Head-to-head data available from MM-020 for Rd and MPT. NMA used for comparison with VMP which was not evaluated in MM-020, as per the reference case.
Assumptions surrounding treatment effect	Non-constant hazards – HRs calculated per 6 months, VMP HRs CIC for OS and for PFS equal to MPT from 24 months (and average HR over the previous 24 months is also equal)	Constant HRs on PFS and OS for VMP vs. MPT, time-varying hazards tested in sensitivity analysis. Relative treatment effect for Rd vs. MPT modelled directly from observed data pre-92 weeks, and assumed constant post-92 weeks	NMA tests for time dependency of relative treatment effects on PFS and OS for VMP vs MPT were statistically insignificant (Section B.2.9). PFS and OS curves for Rd and MPT cross within the first 92 weeks and log-cumulative hazard plots indicate non-proportional hazards post-92 weeks (Section B.2.9)
Source of utilities	Gulbrandsen and colleagues from the mapping by McKenzie and van der Pol. (0.58 for treatment period, and 0.68 for post-treatment)	Rd and MPT use EQ-5D data from MM-020. For VMP, QLQ-C30 data from VISTA [Delforge et al. 2012] were mapped to EQ-5D using Proskorovsky et al. 2014	EQ-5D collected from key clinical trial, as in the reference case, with comparator values taken from trial EORTC-QLQ-C30 data and mapped to EQ-5D, consistent with NICE submission TA228
Source of costs	BNF; MIMS; NHS Reference Costs	eMIT, MIMS; NHS Reference Costs	Consistency with the reference case

Key: BNF, British National Formulary; **HR,** hazard ratio; **PH**, proportional hazards; **MPT,** melphalan, prednisone and thalidomide; **NHS**, National Health Service; **NICE,** National Institute for Health and Care Excellence; **NMA,** network meta-analysis; **PFS,** progression-free survival; **RCT,** randomised controlled trial; **Rd;** lenalidomide and low-dose dexamethasone until disease progression**; TA,** technology appraisal; **VMP,** bortezomib, melphalan and prednisone.

B.3.2.3 Intervention technology and comparators

In line with the final scope, the model conducts pairwise comparisons of Rd with the following comparators;

- Thalidomide in combination with melphalan and prednisone (MPT)
- Bortezomib in combination with melphalan and prednisone (applicable to the subgroup of people who are unable to tolerate, or have contraindications to thalidomide) (VMP)

As described in Table 1, CTD was not considered a relevant thalidomide-based combination as it is unlicensed. MPT was considered a suitable proxy for CTD as it was deemed by clinical specialists who took part in TA228 to be equivalent in terms of efficacy and toxicity, and is also similar in terms of cost.

The doses of the interventions and comparator treatments were implemented as per their marketing authorisations and the clinical trials which inform clinical effectiveness in the economic model (Table 26).

Table 26 Intervention and comparator regimens

Technology	Drug	Dose	Administration	Days	Cycle length (days)	Stopping rule	Source
Rd	Lenalidomide	25 mg once daily	Oral	1 to 21	28	Until progression or unacceptable toxicity	MM-020[31]
	Dexamethasone	40 mg once daily	Oral	1, 8, 15 and 22	28	Until progression or unacceptable toxicity	
MPT	Melphalan	0.25 mg/kg	Oral	1 to 4	42	12 cycles (72 weeks)	
	Prednisone	2 mg/kg	Oral	1 to 4	42	12 cycles (72 weeks)	
	Thalidomide	200 mg	Oral	1 to 42	42	12 cycles (72 weeks)	
VMP	Bortezomib	1.3 mg per m^2	Intravenous	1, 4, 8, 11, 22, 25, 29 and 32 (Cycles 1–4) 1, 8, 22 and 29 (Cycles 5–9)	42	9 cycles (54 weeks)	VISTA[39]
	Melphalan	9 mg per m^2	Oral	1 to 4	42	9 cycles (54 weeks)	
	Prednisone	60 mg per m^2	Oral	1 to 4	42	9 cycles (54 weeks)	

Key: **MPT**, melphalan, prednisone and thalidomide; **Rd;** lenalidomide and low-dose dexamethasone until disease progression; **VMP,** bortezomib, melphalan, and prednisone.

B.3.3 Clinical parameters and variables

The evidence used within the economic model is in line with evidence presented to inform comparative effectiveness (section B.2.6). The comparisons of Rd to MPT were made using head to head data from the MM-020 trial. VMP was incorporated based on the HRs for PFS and OS estimated by the NMAs described in B.2.9.

B.3.3.1 Progression-free and overall survival: Rd and MPT

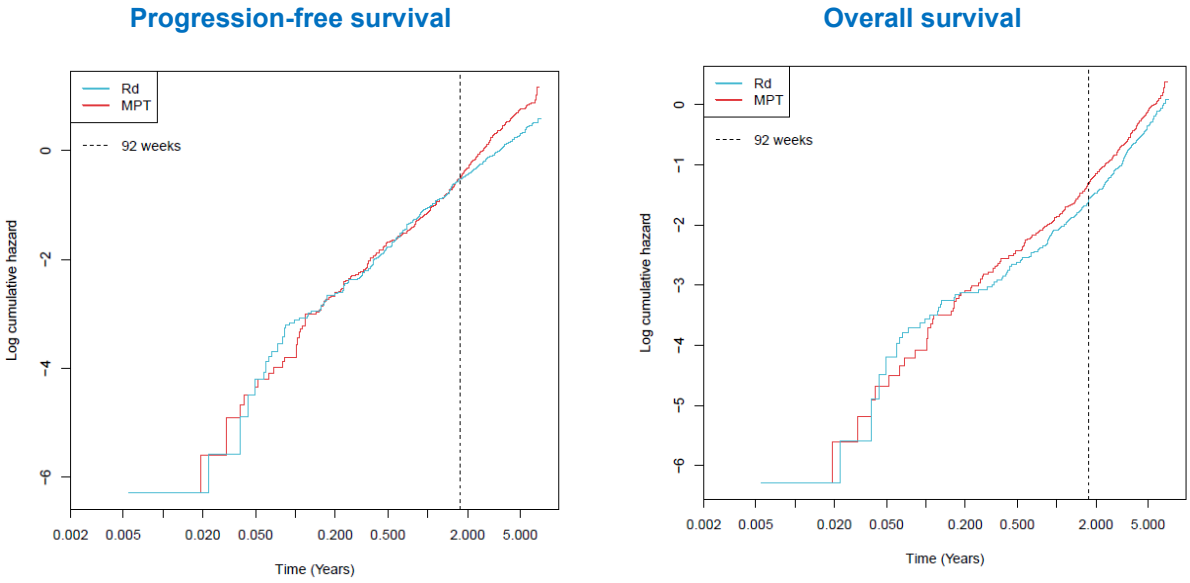
The latest available data for the ITT population from MM-020 were used for Rd and MPT (data cut-off, 21 January 2016).[43,68] Analysis of PFS was based on EMA censoring rules and the investigator's assessment of progression;[68] this was used instead of the IRAC assessment, as the IRAC was disbanded in 2013.

The analysis of OS for the 21 January 2016 data cut-off reported 623 death events across the Rd and MPT treatment arms,[43] which represents 58% of the ITT population. Not every patient in the MM-020 trial was followed until disease progression and/or death; therefore, it is necessary to extrapolate PFS and OS over lifetime.

PFS and OS for Rd and MPT were generated from the individual transitions of the MSM model (Section B.3.2). This analysis was conducted in the R package `msm`.[102]

The PFS hazard was not constant over time. The PFS KM curves from the MM-020 trial for Rd and MPT (Figure 19) overlapped until approximately 92 weeks post-randomisation, after which the curves separate in favour of Rd. The separation of the curves continued to widen with longer follow-up. This delayed treatment effect is also reflected in the log-cumulative hazard plots (Figure 18) and cumulative hazards (Figure 42) for PFS. These plots suggest that the delayed treatment effect for Rd on PFS is driven by an increase in the hazard for MPT rather than a decrease in the hazard for Rd. For OS, the log-cumulative and cumulative hazards plots (Figure 18 and Appendix L, Figure 42) and KM (Figure 19) do not show a similar pattern.

Figure 18: Log-cumulative hazards plot of Rd and MPT



Key: ITT, intent-to-treat; **MPT,** melphalan, prednisone and thalidomide; **Rd;** lenalidomide and low-dose dexamethasone until disease progression.
Note: Data cut-off = 21 January 2016 (ITT population).

This likely reflected the difference in planned treatment duration for the Rd and MPT arms: Rd patients were scheduled to receive treatment until unacceptable toxicity or progressive disease; whereas MPT patients were scheduled to receive treatment for up to 12 42-day cycles (total 72 weeks). It was also considered plausible to have a 20-week treatment effect delay for PFS resulting from discontinuation in the MPT arm. Thus, a 'hybrid' approach with a 92-week 'cut-point' was chosen for modelling these data:

- t < 92-weeks; KM data for PFS and OS were used to represent the proportion of patients in each health state using a partitioned survival methodology. This approach was chosen to provide an accurate reflection of the relative treatment effect of Rd vs. MPT in this interval.
- $t \geq$ 92-weeks; a time-homogeneous MSM model was fitted. Patients still alive at 92 weeks were included in the analysis. As such, the cut-point of 92 weeks was applied to all transitions in the model.

A patient's baseline state ('progression-free' or 'progressed') for the MSM model was derived using a last observation carried forward procedure; the last available state prior to 92 weeks was carried forward to be used as a new baseline. Patients who died or were censored for OS prior to 92 weeks were not included in the MSM analysis.

Log-cumulative hazards of PFS for Rd and MPT showed diverging of curves from 92 weeks, with the assumption of proportional hazards not appearing to hold (Figure 18). The log-cumulative hazards of OS for Rd and MPT were not parallel after 92 weeks, but MSM functionality requires PFS and OS to be modelled simultaneously. Therefore, one set of matrices was generated per arm, rather than including treatment as a covariate. The corresponding transition probabilities are presented in Table 27.

Table 27: MSM probability transition matrices – 28-day probabilities

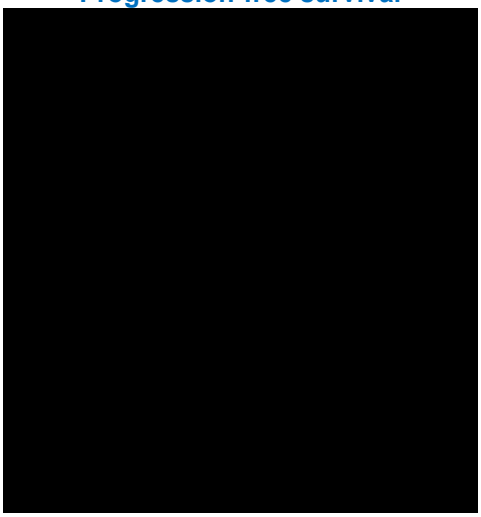
From/to	**Rd**			**MPT**		
	Progression-free	Progressive disease	Death	Progression-free	Progressive disease	Death
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	0	0	1	0	0	1

Key: MPT, melphalan, prednisone and thalidomide; **MSM,** multi-state Markov; **Rd;** lenalidomide and low-dose dexamethasone until disease progression.

Estimates of PFS and OS were calculated using these probability transition matrices (Figure 19; Figure 43 and Figure 44 in Appendix L). It can be observed that the MSM model fits the observed data well post-92 weeks.

Figure 19: KM plots of survival with superimposed MSM model

Progression-free survival



Overall survival

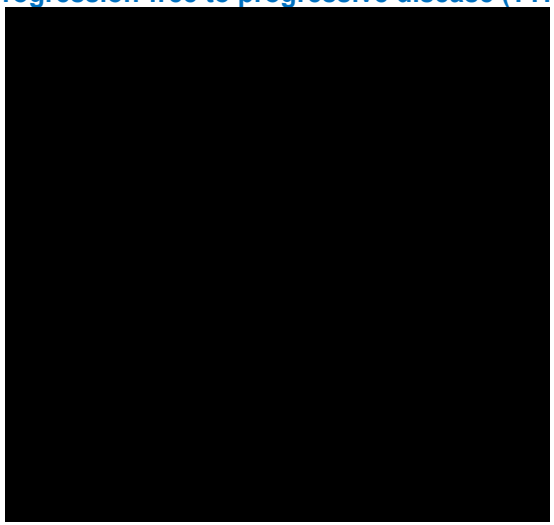
Key: ITT, intent-to-treat; **KM,** Kaplan–Meier; **MPT,** melphalan, prednisone and thalidomide; **MSM,** multi-state modelling; **Rd;** lenalidomide and low-dose dexamethasone until disease progression**; trt,** treatment.
Notes: Data cut-off = 21 January 2016 (ITT population). The final drop in overall survival is due to the number at risk going from 1 to 0 at 85 months.

In line with TSD 19,[100] the fit of the MSM was also assessed for each transition. Mapping individual transitions to the patient-level data is shown in Figure 20:

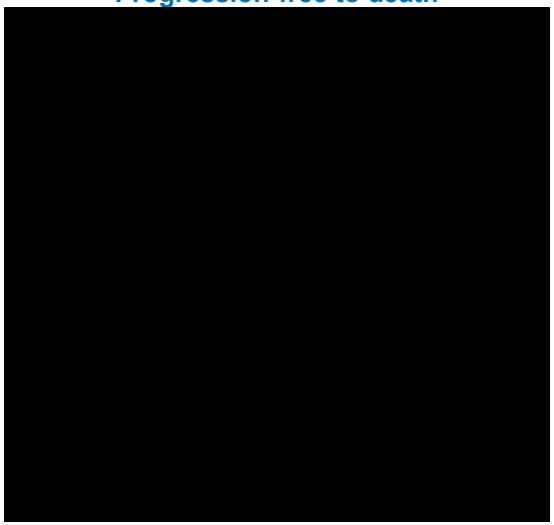
- 'Progression-free' to 'progressive disease': the MSM slightly underestimates the rate of events for both treatments until 4 years, and slightly overestimates at later time points (where there is a reduced number of patients at risk).
- 'Progression-free' to 'death': the MSM fits the observed data reasonably well, with a slight tendency for the MSM to overestimate the rate of events until 4 years, and underestimate the rate of events at later time points (where there is a reduced number of patients at risk).
- 'Progressive disease' to 'death': the MSM fits the observed data well, even when there are a limited number of patients at risk of death. These curves predicted for Rd and MPT lie on top of one another, indicating that PPS is similar for the two treatments (the cycle probabilities for Rd and MPT are [redacted] and [redacted], respectively) (Table 27). This is clinically plausible, as Rd has been accepted to have a post-progression treatment effect due to its immunomodulatory mechanism of action,[55] which could be balanced by the use of subsequent Rd on the MPT arm. A scenario assuming equal post-progression survival for Rd and MPT is tested in sensitivity analysis.

Figure 20: KM plots of health state transitions with superimposed MSM model

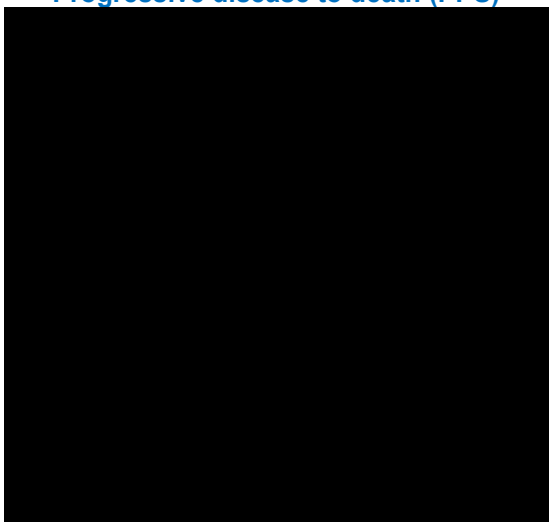
Progression-free to progressive disease (TTP)



Progression-free to death



Progressive disease to death (PPS)



Key: ITT, intent-to-treat; **KM,** Kaplan–Meier; **MPT,** melphalan, prednisone and thalidomide; **MSM,** multi-state modelling; **PPS,** post-progression survival; **Rd;** lenalidomide and low-dose dexamethasone until disease progression**; TTP,** time to progression.

B.3.3.2 Progression-free and overall survival: VMP

To estimate PFS and OS for VMP, HRs for VMP versus MPT from the NMA were applied to the MPT PFS and OS curves predicted by the model (Section B.2.9). The mean HRs for PFS and OS were 1.00 and 1.11 respectively; the corresponding PFS and OS curves are presented in Figure 21.

MPT was chosen as the reference treatment due to the relative maturity of the MPT data which inform the transitions, it also being a fixed-duration therapy and the regimen also including melphalan and prednisone.

Constant HRs are used in the base case hence assuming proportional hazards for VMP vs. MPT, as the time-varying NMA did not predict a statistically significant time dependency in the VMP HRs for PFS and OS (Section B.2.9.2). However, the point estimates of the HR did show some potentially meaningful changes over time. As such, the outputs of the time-varying HRs NMA are used as scenario analyses to test the impact of the proportional hazards assumption for VMP vs. MPT. The only trial in the network containing data on VMP (VISTA) provided maximum follow-up for PFS of 27 months, and the estimated HRs of VMP vs. MPT from the NMA after this point are associated with susbtantial uncertainty. As such, the estimated HRs at the maximum follow-up for each endpoint are applied for lifetime.

Using the constant OS HR from the NMA for VMP vs. MPT of 1.11 yields shorter post-progression survival for VMP than Rd and MPT (given PFS for VMP is equal to MPT). This is likely a consequence of the subsequent therapy use in the VISTA trial compared to MM-020; patients in VISTA received more thalidomide in second-line in comparison to MM-020 where patients received more lenalimdomide and bortezomib (Table 46). A scenario assuming equal OS and equal subsequent treatment use for VMP vs. MPT is modelled in sensitivity analysis.

Figure 21: Modelled progression-free and overall survival

Key: MPT, melphalan, prednisone and thalidomide; **Rd;** lenalidomide and low-dose dexamethasone until disease progression**; VMP,** bortezomib, melphalan and prednisone.
Notes: The constant PFS hazard ratio for VMP versus MPT is 1, so the PFS curves for VMP and MPT overlap completely.

B.3.3.3Accounting for general population mortality

The general population mortality probability per cycle was calculated from national life tables[103] and used as a minimum OS transitions per cycle across all treatment arms. This comes into effect at approximately 19 years for Rd, 21 years for MPT and 23 years for VMP.

B.3.3.4Capturing uncertainty in PFS and OS

Uncertainty in the KM curves for Rd and MPT before the 92-week cut off is captured using a HR calibrated for each KM survival function to the Greenwood's 95% CI.[104] This assumed a normal distribution based on Greenwood's assumption of normally distributed variance, and each HR was calibrated by changing the variance of the normally distributed HR to match the uncertainty of the KM estimate. This method allows uncertainty of survival estimates within the observed trial data to be parameterised and adequately captured, and was previously used in NICE TA384 of nivolumab monotherapy in melanoma.[105]

Uncertainty in the transition probabilities is captured by randomly sampling from a set of 1,000 bootstraps from the MSM analysis. This approach has been used previously in the cost-effectiveness model submitted for the ongoing NICE appraisal of lenalidomide for second-line multiple myeloma (ID667).[106]

Uncertainty in the HR for VMP versus MPT is captured by randomly sampling from a set of 40,000 convergence diagnosis and output analysis (CODA) samples, where the correlation between relative treatment effects in the network is preserved.

B.3.3.5Time on treatment

To calculate the proportion of patients on treatment in each model cycle, patient-level TTF data from the MM-020 trial were used to fit parametric curves for the Rd and MPT arms (Table 28).

Table 28: Parametric curves fitted to time to treatment failure data and their statistical fit

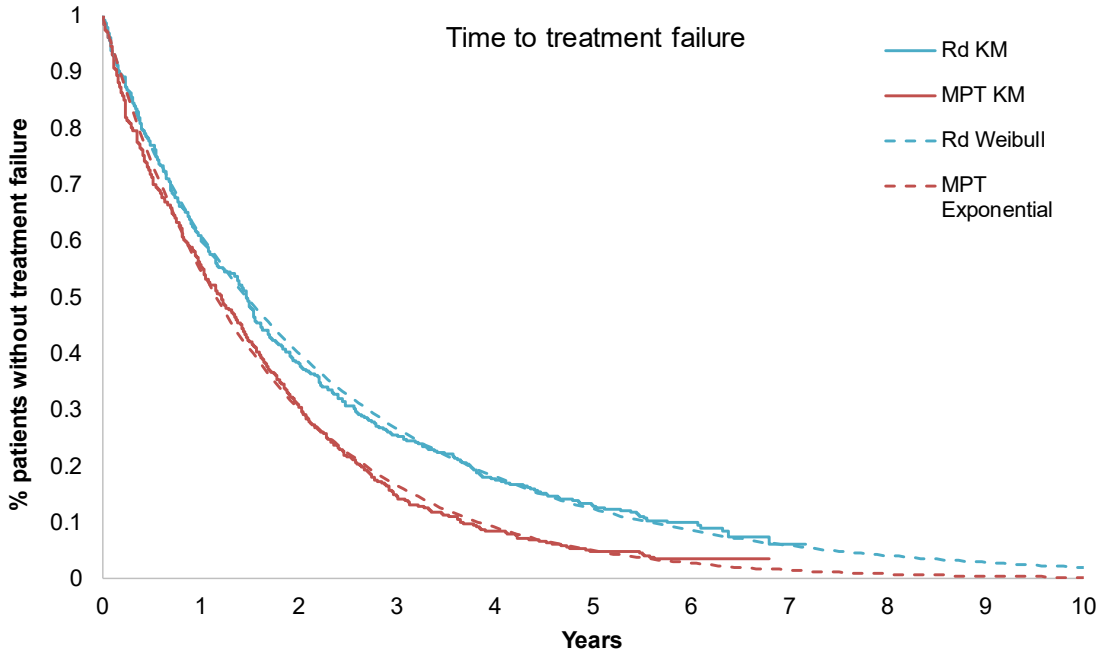
Distribution	Rd		MPT	
	AIC	BIC	AIC	BIC
Exponential	4,163.01	4,167.29	4,200.53	4,204.84
Generalised gamma	4,155.54	4,168.38	4,202.21	4,215.13
Gompertz	4,154.09	4,162.65	4,201.50	4,210.11
Log-logistic	4,171.87	4,180.43	4,259.74	4,268.35
Log-normal	4,188.38	4,196.95	4,296.12	4,304.73
Weibull	4,156.66	4,165.22	4,200.66	4,209.27

Key: AIC, Akaike information criterion; **BIC**, Bayesian information criterion; **MPT**, melphalan, prednisone and thalidomide; **Rd;** lenalidomide and low-dose dexamethasone until disease progression.

Given the maturity of the data available the model is relatively insensitive to the curve fit selected for TTF; the AIC and BIC statistics indicate that the Gompertz, Weibull and exponential distributions are plausible fits for Rd (difference of <5 on fit criteria) and the exponential and Weibull distributions are plausible fits for MPT.

Selecting the parametric curve with the best statistical fit according to BIC for the Rd arm (Gompertz) causes the TTF and PFS curves to cross at approximately 18 years, hence the second-best fitting curve (Weibull) is selected for the base case. For MPT, the best-fitting curve (exponential) is chosen (Figure 22). Time on treatment is capped at 18 cycles for MPT as per the treatment schedule (Table 25).

Figure 22: Time to treatment failure curve fits and KM data



	Number at risk					
Years	0	2	4	6	8	10
Rd	535	204	95	32	0	0
MPT	547	168	46	12	0	0

Key: KM, Kaplan–Meier; **MPT,** melphalan, prednisone and thalidomide; **RD;** lenalidomide and low-dose dexamethasone until disease progression**; VMP,** bortezomib, melphalan and prednisone.
Note: KM data shown are time to treatment failure; completing all 12 MPT treatment cycles does not count as a failure event.

In the absence of patient-level data for VMP, TTF is assumed equal to PFS up to the maximum treatment duration (nine 42-day cycles). This is more conservative than the assumption used in TA228 to estimate VMP treatment costs; in the AG model, the maximum scheduled treatment duration (all patients on nine 42-day cycles) is used for modelling time on treatment, with no correction for progression or discontinuation from treatment.[107] This has been tested in scenario analyses, using assumptions from TA228 and using the TTF:PFS ratio from Rd MM-020 trial data.

B.3.4 Measurement and valuation of health effects

Multiple myeloma is an incurable disease. Maintaining good HRQL is an important goal in the care of people with myeloma, allowing them to make the most of their remaining life.[108] The uncontrolled growth of myeloma cells has many consequences, including skeletal destruction, bone marrow failure, suppression of normal immunoglobulin production and renal insufficiency.[109] Symptoms include:

bone pain, fatigue, infectious complications and reduced physical function and mobility.[108,110] There is evidence that patients with myeloma report more symptoms and problems than those with other haematological cancers.[111]

Section B.1.3.2 provides an overview of MM and its impact on patients and their carers. In addition to physical symptoms, multiple myeloma patients can suffer considerably from fear of recurrence and uncertainty about the future due to the relapsing nature of the disease. Additionally, the complexity, the difficulty of treatment and frustration with the limited treatment options available can combine to lead to patients feeling a loss of independence and inability to plan for the future.[108]

As discussed in B.2.13, lenalidomide is an oral therapy and can therefore be self-administered at home, with only outpatient consultations during treatment. Using an oral agent such as lenalidomide reduces the treatment burden on both patients and carers, relative to IV and SC treatments. This is particularly important for patients with multiple myeloma who are often frail, elderly and have mobility problems related to their condition.[112,113]

B.3.4.1 Health-related quality-of-life data from clinical trials

In MM-020, HRQL was measured using EORTC QLQ-C30, EORTC QLQ-MY20 and the EQ-5D-3L (Section B.2.6.11). MM-020 therefore provides utility data that are consistent with the NICE reference case.

B.3.4.2 Mapping

The data collected in the MM-020 trial using the EORTC QLQ-C30 and QLQ-MY20 were not mapped to estimate health state utilities because EQ-5D data were also available.

B.3.4.3 Health-related quality-of-life studies

The utility data reported by Delforge 2015,[47] the one study identified by the SLR, are not presented here given that this is a subsequent publication of the MM-020 trial, which is discussed in section B.3.4.1.

This was supplemented by a targeted search of ISPOR proceedings and NICE submissions to identify disutilities for subsequent therapy and lines of treatment in multiple myeloma patients. Four articles were found (Table 33), and the impact of their identified subsequent disutilities are tested in scenario analysis. [56,114-116]

B.3.4.4 Adverse reactions

The impact of adverse reactions on HRQL was not modelled separately as differences in HRQL between treatment arms due to adverse reactions are assumed to be captured by the time-dependent treatment covariates used in the 'pre-progression' utility calculations.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Given the model structure, it was necessary to estimate utility values for the following health states:

- Progression-free: this includes first-line treatment and associated AEs
- Progressive disease: this includes second and third-line treatment and associated AEs

B.3.4.5.1 Health state utilities for Rd and MPT

To align with the NICE reference case, the EQ-5D data from MM-020 were used for Rd and MPT. To determine the best predictors of HRQL, several analyses were conducted, including:

- Analysis by progression status
- Analysis by progression status and treatment
    - In the Rd arm, there was 2,239 and 257 non-progressed and progressed observations, respectively
    - In the MPT arm, there was 2,172 and 269 non-progressed and progressed observations, respectively
- Analysis for observations in the non-progressed state according to time since baseline
- Analysis for observations in the non-progressed state according to time since baseline and treatment received

Mixed-effects regression modelling was used to account for autocorrelation (a patient's future EQ-5D scoring is partly predicted by the observations they have already provided).

B.3.4.5.2 Analysis by progression status

Table 29 presents results of the mixed-effects regression analysis of utility by progression status. Progression is predicted to yield a significant but small reduction

in utility (-0.028; p=0.014). This indicates the impact of progressing from first to second-line treatment does not have a substantial impact on patients HRQL as measured within the clinical trial (it should be noted that this is likely a function of the data only covering 1 visit post progression)..

Table 29: Mixed-effects (patient as random effect) regression model results of utility ~progression

Solution for Fixed Effects									
Effect	Progressed	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept		0.5849	0.008397	1056	69.66	<.0001	0.05	0.5685	0.6014
Progressed	1	-0.02754	0.01122	3787	-2.46	0.0141	0.05	-0.04954	-0.00555

Key: DF, degrees of freedom; **Pr,** probability; **SE,** standard error.

B.3.4.5.3 Analysis by progression status and treatment

The regression model with covariates for treatment and progression status is presented in Appendix L, Table 102. Although progression is still seen to cause a significant reduction in utility score (-0.028; p=0.014), the treatment effect for Rd is non-significant (p=0.755), thus the regression model without a treatment covariate (Table 29) is used for all treatments (Rd, MPT and VMP) for their utility in the 'progressive disease' health state.

B.3.4.5.4 Analysis for observations in the 'progression-free' state according to time since baseline

Analysis of utility by time for patients in the 'progression-free' state was conducted by firstly grouping time into categories to define changes in utility over time. A scatter plot of the data divided by the time quartiles is presented in Appendix L, Figure 45. The plot shows a tendency towards increased quality of life as time increases. Data from MM-020 also show that the rate of AEs substantially reduces within both the Rd and MPT arms over time as clinicians are able to identify and manage these events via dose adjustment/concomitant treatment.

The following quartiles were used to group time, based on the number of observations over time:

- Q1: 0.00-4.00 weeks
- Q2: 4.00-12.00 weeks
- Q3: 12.00-28.86 weeks

- Q4: >29.86 weeks

The use of quartiles was preferred over continuous time as it is unlikely that treatment will have a continuous positive impact in the long term on patients' quality of life after the observations within the clinical trial, and performing the analysis using time as a continuous variable did not provide a significant effect. The use of this method also allows the influence of short-term treatment related AEs for patients receiving high-dose treatment to be separated from the long-term disease control effects of treatments. Quartiles were chosen purely on a mathematical basis, i.e. during the first quartile (the first 4 weeks), a quarter of the total HRQL measurements were taken.

B.3.4.5.5 Analysis for observations in the 'progression-free' state according to time since baseline and treatment received

Appendix L, Table 103 presents the regression analysis results for utility in non-progressed patients against time quartiles and treatment. The utility score is seen to significantly increase over time in Q2, Q3 and Q4. Patients who received Rd had a small increase in utility score (0.006) compared to MPT; although again this result is non-significant (p=0.718).

Table 30 presents the regression analysis results for utility in progression-free patients against time quartiles and treatment with an interaction between the time quartiles and treatment. The interaction term was not significant for all time points (interaction p= 0.4229) indicating that treatment effects do not significantly change over time. Although this interaction is not significant, this is included in the base case as individual AE quality of life impacts associated with each treatment are not modelled separately, and this interaction is expected to capture any treatment-specific adverse event disutilities. The intercept and coefficient inputs are tested in one-way and PSA using a multivariate normal distribution, with the treatment effect and interaction terms removed in scenario analysis.

Table 30: Mixed effects (patient as random effect) regression model results of utility ~ time quartiles (categorical) + treatment + (time quartiles [categorical]*treatment) (interaction)

Solution for Fixed Effects										
Effect	**timeQ**	**Treatment**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**	**Alpha**	**Lower**	**Upper**
Intercept			0.5189	0.01424	1054	36.43	<.0001	0.05	0.4909	0.5468
timeQ	Q2		0.04964	0.01418	3275	3.50	0.0005	0.05	0.02185	0.07744
timeQ	Q3		0.09003	0.01327	3275	6.78	<.0001	0.05	0.06400	0.1161
timeQ	Q4		0.1266	0.01415	3275	8.95	<.0001	0.05	0.09883	0.1543
timeQ	Q1		0	.	.	.	.	.	.	.
trtf		Rd	0.001768	0.01995	3275	0.09	0.9294	0.05	-0.0374	0.04089
timeQ*trtf	Q2	Rd	-0.01286	0.01996	3275	-0.64	0.5193	0.05	-0.0520	0.02627
timeQ*trtf	Q3	Rd	0.01805	0.01842	3275	0.98	0.3271	0.05	-0.0181	0.05416
timeQ*trtf	Q4	Rd	0.008863	0.01955	3275	0.45	0.6503	0.05	-0.0295	0.04719

Key: DF, degrees of freedom; **MPT,** melphalan, prednisone and thalidomide; **Pr,** probability; Q, quartile; **Rd;** lenalidomide and low-dose dexamethasone until disease progression; **timeQ**, time quartile; trtf, treatment.

3.4.5.5.1 Health state utility values for VMP

For VMP, published HRQL results from the VISTA trial were used.[46] In this published report, the authors provided the EORTC QLQ-C30 mean functional and symptom scores (stratified by treatment) for all randomised participants in the VISTA trial taken over the 9 cycles of treatment and at the end-of-treatment visit. The mean relevant domain scores for all visits in the progression-free phase were extracted and mapped onto EQ-5D values; the mapping was based on a published algorithm developed from data for 159 patients with MM.[117]

Based on the derived mean EQ-5D values, changes in utility values from baseline during the 'progression-free' state over time were estimated (Table 31). Compared with the treatment-specific utility values for Rd, the utility values for VMP are often lower during the first several cycles of treatment (Figure 23). This is consistent with the fact that HRQL (based on the published data from the VISTA trial) was compromised during the VMP treatment phase.[46] In the base case, the model assumes equal baseline utility for VMP and Rd to not induce bias in the cost-effectiveness estimates.

Table 31: VMP 'progression-free' utility relative to baseline over time

Cycle (per 4 weeks)	**Mapped utility score from VISTA**	**Change from baseline**	**Modelled change from baseline**		**Estimated value for VMP assuming 0.53 at baseline***
			Rd	**MPT**	
1	0.507	+0.000	+0.000	+0.000	0.521

2	0.527	+0.020	+0.037	+0.050	0.541
3	0.514	+0.007	+0.037	+0.050	0.527
4	0.504	-0.004	+0.108	+0.090	0.517
5	0.536	+0.029	+0.108	+0.090	0.549
6	0.579	+0.072	+0.135	+0.127	0.592
7	0.605	+0.098	+0.135	+0.127	0.619
8	0.621	+0.114	+0.135	+0.127	0.634
Thereafter	0.632	+0.125	+0.135	+0.127	0.645

Key: MPT, melphalan, prednisone and thalidomide; **Rd;** lenalidomide and low-dose dexamethasone until disease progression; **VMP,** bortezomib, melphalan and prednisone.

Notes: *Consistent with the MPT and Rd arms, taken from the MM-020 trial

The utility values used in this analysis are consistent with those used by the NICE Assessment Group (AG) in the economic model developed in TA228 to assess the cost-utility of frontline MPT and VMP for the same patient population (Table 32). The AG also mapped EORTC QLQ-C30 data to EQ-5D utilities, using two different algorithms;[94] the utility for on treatment was 0.58, taken from the Month 1 value. For off-treatment, it is unclear what was used due to reporting (in one place the report refers to both the use of an average of Month 6 to 36 (0.68) and a figure taking into account response levels, but this is marked CIC). The change between the TA228 values of 0.58 (on treatment) to 0.68 (off treatment) is reflective of the change from baseline utility to after 8 cycles in the model base case (+0.125), although slightly higher, which may bias in favour of VMP (Table 30.).

Table 32: EQ-5D values derived by mapping the EORTC QLQ-C30 scores from Gulbrandsen et al.[110] by the NICE ERG in TA228

Source, algorithm	Time (months [change from baseline])	
	On treatment/ baseline	Off treatment/ after 8 cycles
TA228, McKenzie and van der Pol[118]	0.580	0.683* (0.103)
TA228, Kontodimpoulous et al.[119]	0.580	0.695* (0.115)
Model base case, Proskorovsky et al.[117]	0.530	0.655 (0.125)

Key: EORTC QLQ-C30, EORTC Quality of Life Questionnaire – Core 30; **EQ-5D,** 5-dimension European Quality of Life questionnaire; **ERG,** evidence review group; **Rd;** lenalidomide and low-dose dexamethasone until disease progression. Notes: *, Off treatment calculated using an average of values from Month 6, 12, 24 and 36 from TA228.

3.4.5.5.2 Progressed utility and subsequent treatment utilities

In the base case, the utility of progressed patients is independent of treatment arm

and time (Section 3.4.5.5.3) and is based on an analysis of the EQ-5D data from MM-020 (0.5574, Table 29), as per the NICE reference case.[31]

Given the lack of long-term data post-progression, an option is built into the model to use a subsequent treatment decrement identified from the literature, for patients at second-line and third-line or greater. If this option is selected, the utility for 'progressive disease' is calculated using the 'progression-free' utility for that time point, with a disutility applied for the relevant line of treatment (Table 33). These values were identified by targeted searching of NICE submissions and ISPOR presentations in MM within the last 2 years and recent publications for utilities of multiple myeloma patients disaggregated by treatment line.

Four options are available from the identified literature (Table 33). Hatswell et al.[116] was considered the most appropriate due to the comparability of the 1L utilities to MM-020 and the study using UK patients. In the model, this disutility is applied to the number of patients in second- or third-line therapy which is calculated using the fatal progression rate from the MSM analysis (transition from 'progression-free' to 'death') and the rate of progression at second line, calculated from MM-020 trial data (Table 43). For VMP, rates are assumed equal to MPT in the absence of patient-level data. Using values from Hatswell et al. results in an increase in mean post-progression utility decrement of 0.033 for Rd, 0.028 for MPT and 0.041 for VMP relative to the base case utility as Hatswell et al. predicts no decrement for progression from first to second-line treatment.

Table 33: Literature sourced subsequent treatment utilities

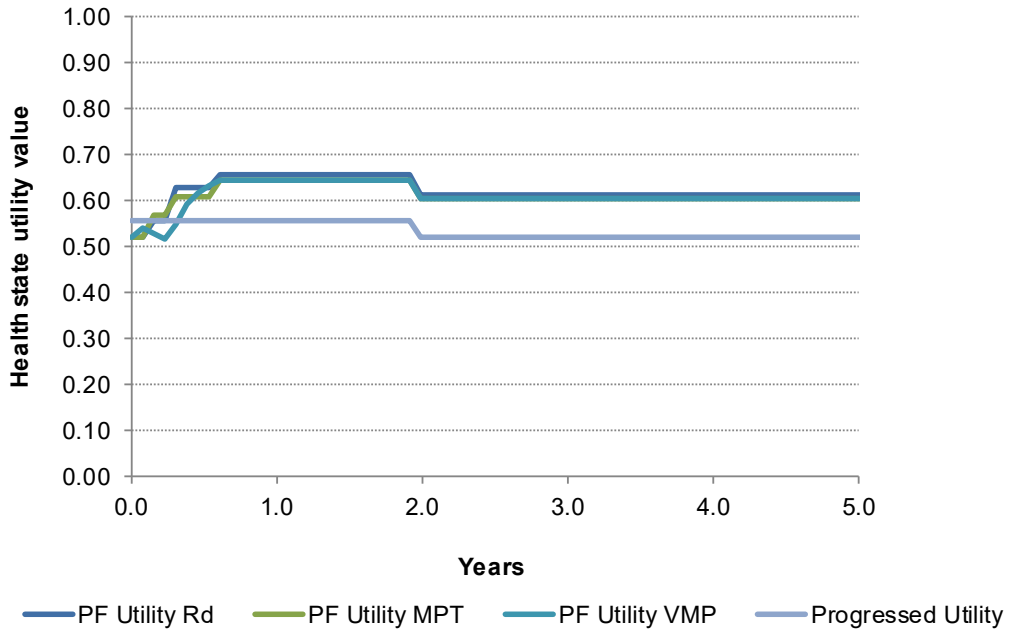
	Publication					
	Hatswell et al. 2016[116]	**Despiegel et al. 2016[114]**	**NICE, TA380 (Patients received at least one prior therapy)**		**ID934**	
1L	0.59	0.67	PrePS, no treatment	0.762		
2L	0.59	0.62	PrePS, PANO/BTZ/DEX	0.706	PrePS (2nd line)	0.810
3L	0.51	0.53	PrePS, BTZ/DEX	0.725	PPS	0.695
4L	0.51	0.48	PPS, LEN/DEX	0.64	PPS	0.640
5L +	0.51	0.48	PPS, LLoT	0.64		
Subsequent treatment decrement						
2L	0	-0.05	2L, PANO/BTZ/DEX	-0.056	2L	NR
			2L, BTZ/DEX	-0.037		
3L	-0.08	-0.09	3L	-0.122	3L	-0.115

Key: BTZ, bortezomib; **DEX,** dexamethasone; **LEN,** lenalidomide; **LLoT,** last line of treatment; **NICE,** National Institute of Health and Care Excellence; **NR,** not reported; **PANO,** panobinostat; **PPS,** post-progression; **PrePS,** pre-progression.

3.4.5.5.3 Age-adjusted utilities

Utilities are adjusted by average age of the patients in the model using the age-banded utility values from Kind et al.[120] As the average age of patients in the model is 73, the utilities are only adjusted once, as patients move from the 65–74 age bracket, to the 75+ age bracket. The 'progression-free' utility for each treatment arm and the 'progressive disease' are plotted over time in Figure 23.

Figure 23: Health state utility values over time



Key: MPT, melphalan, prednisone and thalidomide; **PF,** progression-free; **Rd;** lenalidomide and low-dose dexamethasone until disease progression**; VMP**, bortezomib, melphalan and prednisone.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

The NHS schedule of reference costs was appropriate for costing as the clinical management of the condition is currently costed in the NHS in terms of reference costs.

B.3.5.1 Intervention and comparators' costs and resource use

The patient characteristics used for dosing (including subsequent therapies) according to the product SmPC are presented in Table 34; these data were sourced from the MM-020 trial.

Table 34: Patient baseline characteristics

Characteristic	Value at baseline
Mean body surface area	1.73 m^2
Mean weight	71.5 kg
Percentage of patients with normal renal function	68.6%[43]
Percentage of patients with moderate renal impairment	22.9%[43]
Percentage of patients with severe renal impairment	8.5%[43]
Percentage of patients with age > 75 years	34.9%[43]
Percentage of patients with age ≤ 75 years	65.1%[43]
Percentage of patients with ANC ≥ 1,500	68.7%[43]
Percentage of patients with ANC < 1,500	31.3%[43]

Key: ANC, absolute neutrophil count.

In the base case, dosing data has been taken directly from MM-020 for Rd and MPT to align drug cost with the effectiveness data. Specifically, the observed number of patients on each dosage of each drug at every cycle was combined with unit drug costs to give a weighted cost per cycle. This is multiplied by the proportion of patients eligible for treatment (have not yet failed treatment) who receive treatment in that cycle. In contrast to using mean RDIs, this method accurately captures the impact of treatment reductions or missed treatment cycles over time on costs.

The patients eligible for treatment for each cycle is calculated based on the TTF KM curves shown in Section B.3.3. For oral therapies, only patients missing a whole pack are assumed to have 0 cost for treatment for that cycle. The mean treatment cycle length was also derived directly from the clinical trial data; in the majority of cases the mean treatment cycle length for both Rd and MPT were slightly greater than the 28 days/42 days stated in the product SmPCs due to missed doses or delayed doses within cycle (Appendix L). Consequently, a drug cost is not applied in some model cycles in order to match the number of treatments given in the trial.

In the absence of per cycle dosing data on VMP, the proportion of eligible patients on Rd treatment at each 42-day cycle was used to estimate VMP costs to avoid bias from assuming that all doses of VMP are administered.

For the sensitivity analysis, mean RDIs from the CSRs of MM-020[43] and MM-003,[121] MM-009/MM-010[122,123] and one trial publication for thalidomide were used.[124] VMP RDI was assumed to be equal to that of Rd (Table 36) for this analysis.

Drug costs were taken from eMIT where available, or MIMS, in line with NICE guidance (Table 35).

Table 35: First-line drug costs

First Line Regimens (Trial data: Rd and MPT)					
Treatment Name	**Drug**	**Dose**	**Unit**	**Pack size**	**List price**
Rd	Lenalidomide	2.5	mg	21	£3,426.00[125]
	Lenalidomide	5.0	mg	21	£3,570.00
	Lenalidomide	10.0	mg	21	£3,780.00
	Lenalidomide	15.0	mg	21	£3,969.00
	Lenalidomide	20.0	mg	21	£4,168.00
	Lenalidomide	25.0	mg	21	£4,368.00
	Dexamethasone	20.0/40.0	mg	50x2	£28.93[126]
MPT	Thalidomide	50.00	mg	50	£298.48[125]
	Melphalan	0.25	mg/kg	25x2	£45.38[125]
	Prednisolone	2.0	mg/kg	56x25	£26.19[126]
VMP	Bortezomib	1.3	mg/m^2	3.5	£762.38[125]
	Melphalan	9	mg/m^2	25x2	£45.38[125]
	Prednisone	60	mg/m^2	56x25	£26.19[126]

Key: Rd, lenalidomide and low dose dexamethasone until disease progression; **MPT**, melphalan with prednisone and thalidomide; **mg**, milligrams; MIMS, Monthly Index of Medical Specialities.

For lenalidomide- or thalidomide-containing regimens, patients take aspirin or enoxaparin sodium to prevent venous thromboembolism, and patients receiving bortezomib-containing regimens take acyclovir to prevent herpes. G-CSF is taken to improve the patients' immune system while taking immunomodulatory drugs, and usage for Rd and MPT were taken from the MM-020 CSR.[43] As dosing data were not available for VMP, the base case assumes equivalence to Rd, with equivalence to MPT tested in sensitivity analysis.

A PAS has also been offered for lenalidomide in which the cost of lenalidomide is capped at [redacted] cycles, after which point Celgene bears the cost and the drug is free to the NHS. Each cycle is lasts 28 days. The impact of this PAS is not included in Table 35 and Table 36 above and is instead applied by reducing the drug cost of lenalidomide to zero from the point at which the PAS is applied within the economic model. A per cycle cost is included in the model for applying the PAS to account for the administrative burden of the scheme. This is based on the patient burden per centre and cost of pharmacist time, totalling £22.60 per model cycle (28 days).

Data used to calculate first-line drug costs, prophylaxis regimens and use of granulocyte-colony stimulating factors (G-CSF) are available in Table 35 and Table 36.

VMP is associated with an administration cost of £361 per day, sourced from the National Schedule of Reference Costs 2015-16 (SB15Z).[127] As Rd and MPTs are administered orally, no administration cost is applied.

Table 36: First-line and prophylaxis regimen drug costs

Drug	Dose	% of pts starting dose	Tx cycle length	No. doses /cycle	Cost per package[a]	mg per pill/vial[1]	Pills/vials per package[a]	Mean RDI*	Weighted cost per model cycle
First Line Regimens (RDI Data)									
Rd									
Lenalidomide	25 mg[b]	[redacted]	28[b]	21[b]	£ 4,368.00	25 mg	21	[redacted]	
Lenalidomide	15 mg[b]	[redacted]	28[b]	11[b]	£ 3,969.00	15 mg	21	[redacted]	[redacted]
Lenalidomide	10 mg[b]	[redacted]	28[b]	21[b]	£ 3,780.00	10 mg	21	[redacted]	
Dexamethasone	40 mg[b]	[redacted]	28[b]	4[b]	£ 23.13	2 mg	50	[redacted]	[redacted]
Dexamethasone	20 mg[b]	[redacted]	28[b]	4[b]	£ 23.13	2 mg	50	[redacted]	
VMP									
Bortezomib (First 4 Cycles)	1.3 mg/m[a c]	100%	42[c]	8[c]	£ 762.38	3.5 mg	1	[redacted]	[redacted]
Bortezomib (Cycles 5-9)	1.3 mg/m[a c]	100%	42[c]	4[c]	£ 762.38	3.5 mg	1	[redacted]	[redacted]
Melphalan	9.0 mg/m[a c]	100%	42[c]	4[c]	£45.38	2 mg	25	84%[d]	£34.10
Prednisone	60 mg/m[a c]	100%	42[c]	4[c]	£75.00	25 mg	56	96%[d]	£14.28
MPT									
Melphalan	0.25 mg/kg[b]	100%	42[b]	4[b]	£ 45.38	2 mg	25	84%[b]	£19.38
Prednisolone	2 mg/kg[b]	100%[b]	42[b]	4[b]	£ 75.00	25 mg	56	96%[b]	£12.94
Thalidomide	200 mg[b]	59%[b]	42[b]	42[b]	£ 298.48	50 mg	28	71.6%[b]	£747.91
Thalidomide	100 mg[b]	41%[b]	42[b]	42[b]	£ 298.48	50 mg	28	71.6%[b]	
Prophylaxis Regimens									
VTE									
Aspirin	75 mg	90%	28	28	£ 0.73	75 mg	28	100%[d]	£ 0.66

Enoxaparin Sodium	30 mg	10%	28	28	£30.27	40 mg	10	100%[d]	£ 6.35
Herpes									
Aciclovir	400 mg	100%	28	28	£ 3.02	400 mg	56	100%[d]	£ 1.50
Granulocyte-colony stimulating factor (G-CSF)									
Drug	**Dose as sold**	**Unit**	**Pack cost**	**Pack size**	**Cost per unit**	**Dosing**	**Dose applied**	**Cost per dose**	
Filgrastim	30000000.0	MU/ml	£263.52[a]	5	£0.00	500,000 units/kg	38950000	£68.43	

Treatment	**Patients receiving G-CSF during Active Treatment Phase (%)**	**Instantaneous rate**	**Patients receiving G-CSF per cycle (%)**	**Cost per cycle**
Rd	17.50%[b]	13.89%	1.06%	£0.72
MPT	34.80%[b]	30.89%	2.34%	£1.60
VMP	17.50%[d]	13.89%	1.06%	£0.72

Key: G-CSF, granulocyte colony stimulating factor; **kg,** kilograms; mg, milligram; **MPT,** melphalan, prednisone and thalidomide; **No,** number; **Rd,** lenalidomide and low-dose dexamethasone until disease progression; **RDI,** relative dose intensity; **Tx,** treatment; **VTE,** venous thromboembolism; **VMP,** bortezomib, melphalan and prednisone.
Note: [a], Source: MIMs, Accessed Jan 2017[125]; [b], Source: MM-020 CSR, 2016.[43]; [c], Source: VISTA – San Miguel et al., 2008[39]; [d], Assumption; [e], includes administration cost; *, trial dosing for first-line regimens, rather than RDI, is applied in the base case.

B.3.5.2 Health-state unit costs and resource use

All health state costs in the model are captured in first-line drug costs, AE management, laboratory tests and monitoring, prophylactic treatments and post-progression treatment costs (Table 37).

In pre-progression, patients will accrue resource use costs (comprising health care visits and assessments), and if they are on treatment, they will accrue prophylaxis, AE and first-line treatment costs. In post-progression, patients will accrue weekly resource use costs and upon progression, patients will accrue one-off subsequent treatment costs.

Table 37 Health state costs

Health states	Items	Value (per cycle)			
		Rd	MPT	VMP	Reference in submission
Pre-progression	First-line treatment*	[redacted]	[redacted]	[redacted]	Table 36
	G-CSF	[redacted]	[redacted]	[redacted]	Table 36
	Prophylaxis	[redacted]	[redacted]	[redacted]	Table 36
	Adverse event (First cycle)	[redacted]	[redacted]	[redacted]	Table 38 and Table 39
	Health visits & assessments	[redacted]	[redacted]	[redacted]	Table 40, Table 41 and Table 42
	Total	[redacted]	[redacted]	[redacted]	
Post-progression	Subsequent treatment (2L)	[redacted]	[redacted]	[redacted]	Table 44, Table 45 and Table 46
	Subsequent treatment (3L)	[redacted]	[redacted]	[redacted]	Table 44, Table 45 and Table 46
	Health visits & assessments	[redacted]	[redacted]	[redacted]	Table 40, Table 41 and Table 42
	Total	[redacted]	[redacted]	[redacted]	
Death	N/A	N/A	N/A	N/A	Assumption given lack of robust data for terminal care costs in MM, and expected immaterial impact on the ICER

Key: 2L, second line; **3L,** third line; **G-CSF**, granulocyte-colony stimulating factor; **MPT,** melphalan, prednisone and thalidomide; **Rd,** lenalidomide and low-dose dexamethasone until disease progression; **VMP,** bortezomib, melphalan and prednisone.

Notes: *, including administration costs and using trial dosing. Based on [redacted] model cycles for lenalidomide,18 for MPT and 13 for VMP.

B.3.5.3 Adverse reaction unit costs and resource use

Costs associated with managing Grade 3 and 4 AEs that occurred during the treatment phase in ≥ 5% of patients were included in this analysis. Frequencies were taken from the MM-020 trial for Rd and MPT,[43] and from VISTA for VMP[70] (Table 38).

Costs per each AE were derived from the NHS National Schedule of Reference Costs for 2015-2016.[127] When healthcare resource groups (HRGs) were used, day case codes were assumed (except for hyperglycaemia, where non-elective inpatient short stay was assumed). The costs per event used in the model are shown in Table 39.

Table 38: AE frequency by treatment arm and cycle

	Cycles* 0–6			Cycles* 7–12			Cycles* 13–18			Cycles* >18		
AE	**Rd**	**MPT**	**VMP**	**Rd**	**MPT**	**VMP**	**Rd**	**MPT**	**VMP**	**Rd**	**MPT**	**VMP**
Neutropenia	0.812	2.352	0.331	0.580	1.050	0.331	0.435	0.574	0.331	0.225	0.024	0.331
Anaemia	0.489	0.549	0.168	0.175	0.118	0.168	0.186	0.054	0.168	0.058	0.004	0.168
Thrombocytopenia	0.224	0.219	0.216	0.250	0.210	0.216	0.205	0.236	0.216	0.046	0.000	0.216
Lymphopenia	0.196	0.252	0.146	0.020	0.248	0.146	0.025	0.061	0.146	0.013	0.004	0.146
Leukopenia	0.139	0.396	0.228	0.090	0.129	0.228	0.075	0.081	0.228	0.012	0.020	0.228
Pneumonia	0.073	0.120	0.050	0.050	0.038	0.050	0.056	0.007	0.050	0.031	0.000	0.050
Asthenia	0.114	0.083	0.060	0.070	0.059	0.060	0.062	0.027	0.060	0.031	0.000	0.060
Fatigue	0.090	0.111	0.070	0.040	0.054	0.070	0.056	0.014	0.070	0.048	0.004	0.070
Hypokalaemia	0.102	0.062	0.060	0.035	0.016	0.060	0.025	0.000	0.060	0.043	0.000	0.060
Hyperglycaemia	0.094	0.037	0.000	0.075	0.022	0.000	0.012	0.000	0.000	0.010	0.000	0.000
Back pain	0.139	0.103	0.000	0.010	0.022	0.000	0.019	0.014	0.000	0.038	0.000	0.000
Dyspnoea	0.053	0.078	0.000	0.015	0.011	0.000	0.037	0.000	0.000	0.018	0.000	0.000
Peripheral sensory neuropathy	0.000	0.050	0.135	0.005	0.156	0.135	0.012	0.182	0.135	0.005	0.004	0.135
Constipation	0.033	0.116	0.000	0.005	0.005	0.000	0.006	0.007	0.000	0.003	0.000	0.000
Deep vein thrombosis	0.086	0.050	0.000	0.030	0.011	0.000	0.012	0.000	0.000	0.003	0.000	0.000
Rash	0.171	0.124	0.000	0.000	0.005	0.000	0.000	0.000	0.000	0.003	0.000	0.000
Cataract	0.008	0.012	0.000	0.030	0.005	0.000	0.062	0.000	0.000	0.050	0.000	0.000

Key: AE, adverse event; **MPT,** melphalan, prednisone and thalidomide; lenalidomide and low-dose dexamethasone until disease progression; **VMP,** bortezomib, melphalan and prednisone.

Note: *, cycle length of 28 days.

Table 39: AE costs per event

AE	Cost	HRG code	Description
Neutropenia	£326	SA08J	Other Haematological or Splenic Disorders, with CC Score 0–2. Unit day case cost
Anaemia	£326	SA08J	Other Haematological or Splenic Disorders, with CC Score 0–2. Unit day case cost
Thrombocytopenia	£325	SA12K	Thrombocytopenia with CC Score 0–1. Unit day case cost
Lymphopenia	£326	SA08J	Other Haematological or Splenic Disorders, with CC Score 0–2. Unit day case cost
Leukocytopenia	£326	SA08J	Other Haematological or Splenic Disorders, with CC Score 0–2. Unit day case cost
Pneumonia	£167	OPATT: 300	General Medicine. Total Unit Cost
Asthenia	£167	OPATT: 300	General Medicine. Total Unit Cost
Fatigue	£167	OPATT: 300	General Medicine. Total Unit Cost
Hypokalaemia	£299	KC05N	Fluid or Electrolyte Disorders, without Interventions, with CC Score 0–1. Unit day case cost
Hyperglycaemia	£400	KB02K	Diabetes with Hyperglycaemic Disorders, with CC Score 0–1. Non-elective inpatient: short stay cost
Back Pain	£177	OPATT: 191	Pain Management. Consultant-led outpatient attendances, Non-Admitted Face to Face Attendance, First
Dyspnoea	£460	DZ19N	Other Respiratory Disorders with CC Score 0–4. Unit day case cost
Peripheral sensory neuropathy	£176	OPATT: 400	Neurology. Total Unit Cost
Constipation	£167	OPATT: 300	General Medicine. Total Unit Cost
Deep vein thrombosis	£161	OPATT: 303	Clinical Haematology. Total Unit Cost
Rash	£454	JD07K	Skin Disorders without Interventions, with CC Score 0–1. Unit day case cost
Cataract	£403	BZ24G	Non-Surgical Ophthalmology without Interventions, with CC Score 0–1. Unit day case cost

Key: AE, adverse event; **CC**, clinical complications; **HRG,** healthcare resource group.

B.3.5.4 Miscellaneous unit costs and resource use

To calculate the cost per year for routine laboratory tests and monitoring, the number of assessments per year for each first-line treatment (and for the pooled subsequent lines) and the unit cost per each resource are needed. The assessments per year were obtained from a questionnaire (blank questionnaire is presented in Appendix I Figure 37). The questionnaire was completed by seven UK clincians in 2015, who were asked to provide annual rates of laboratory tests and monitoring patterns for

Rd, MPT and VMP and subsequent lines (i.e. post-progression). The averaged responses were used in the model (Table 40).

Resource use during the progression-free phase was specific to the first-line treatment because the level of utilisation on each item depends on treatment regimen. Monitoring patterns and costs were assumed to be constant following progression and the same regardless of first-line treatment.

Table 40: Routine laboratory tests and monitoring procedures patterns per year

	First line			Subsequent lines
Laboratory test or monitoring procedure	**Rd**	**MPT**	**VMP**	
Oncologist/haematologist visits	10.71	9.14	12.50	9.00
Routine blood counts	11.14	9.14	16.00	13.68
Clotting	1.00	1.14	1.17	1.67
International normalized ratio	0.57	0.57	0.67	1.10
Biochemistry (U&Es)	11.43	8.86	14.83	13.55
Liver function tests	10.29	8.00	13.00	11.77
Erythrocyte sedimentation rate	0.71	0.71	0.83	1.10
Plasma viscosity	0.64	0.50	0.75	0.77
Uric acid	1.14	1.11	1.33	1.62
Immunoglobulin	7.14	6.29	7.17	8.17
Paraprotein measurements	9.86	8.57	9.00	9.83
Protein electrophoresis	8.00	7.14	8.17	9.17
Serum β2 microglobulin	1.29	1.29	1.33	2.33
C-reactive protein	3.86	3.14	2.50	3.88
Serum erythropoietin level	0.30	0.30	0.35	0.75
Immunofixation	2.86	2.86	3.17	3.83
Creatinine-clearance	4.36	2.93	3.92	4.68
Routine urinalysis	2.00	1.86	2.17	3.07
24-hour urine measurement	0.79	0.64	0.75	1.17
24-hour urine for creatinine	0.29	0.21	0.33	0.40
Total urine protein	0.71	0.71	0.83	1.20
Urine protein electrophoresis/light chains	2.14	2.00	2.17	2.82
Urine immunofixation	1.00	1.00	1.00	1.02
Skeletal Survey by X-Ray	0.86	0.86	0.83	0.82
Skeletal survey by X-ray individual sites	0.90	0.90	1.05	1.18
Magnetic resonance imaging	0.93	0.93	0.92	1.03
Bone densitometry	0.14	0.14	0.17	0.18
Bone marrow aspirate	1.57	1.43	1.67	1.60
Bone marrow trephine biopsy	0.86	0.86	1.00	1.20
Bacterial investigation	1.79	1.93	2.25	2.52
Calcium	11.43	9.57	13.50	9.43

Albumin	11.43	9.14	13.00	12.77
Lactate dehydrogenase	2.43	2.29	3.17	3.43

Key: MPT, melphalan, prednisone and thalidomide; **Rd,** lenalidomide and low-dose dexamethasone until disease progression; **U&Es,** urea and electrolytes; **VMP**, bortezomib, melphalan and prednisone.

Platelet and red blood cell transfusions are accounted for separately using data from the MM-020 CSR.[43] For VMP, rates for RBC transfusions were taken from NICE TA228 Assessment Report[3] as the percentage of patients requiring transfusions. For platelet transfusion, the base case assumes equivalence to Rd (Table 41).

Table 41: Transfusion rates

Procedure	Rd	MPT	VMP
RBC transfusion	0.20	0.20	0.29
Platelet transfusion	0.11	0.09	0.11

Key: MPT, melphalan, prednisone and thalidomide; **RBC,** red blood cell; **Rd,** lenalidomide and low-dose dexamethasone until disease progression; **VMP,** bortezomib, melphalan and prednisone.

Unit costs for each routine laboratory test were obtained from the 2015–2016 national schedule of reference costs.[127] The national average unit cost, currency code, and description for each test and procedure is shown in Table 42.

Table 42: Routine laboratory tests and monitoring procedures unit costs

Laboratory test or monitoring procedure	National average unit cost	Currency code	Description	Source file
Oncologist/haematologist visits	£166	303	Clinical haematology: face-to-face follow-up attendance	Consultant-led outpatient attendances
Routine blood counts	£3.10	DAPS05	Haematology	Directly accessed pathology services
Clotting	£3.10	DAPS05	Haematology	Directly accessed pathology services
International normalized ratio	£3.10	DAPS05	Haematology	Directly accessed pathology services
Biochemistry (urea and electrolytes)	£5.90	DAPS04	Clinical biochemistry	Directly accessed pathology services
Liver function tests	£8.28	DAPS04	Clinical biochemistry	Directly accessed pathology services
Erythrocyte sedimentation rate	£3.10	DAPS05	Haematology	Directly accessed pathology services
Plasma viscosity	£1.18	DAPS04	Clinical biochemistry	Directly accessed pathology services
Uric acid	£1.18	DAPS04	Clinical biochemistry	Directly accessed pathology services
Immunoglobulin	£1.18	DAPS04	Clinical biochemistry	Directly accessed pathology services
Paraprotein measurements	£1.18	DAPS04	Clinical biochemistry	Directly accessed pathology services
Protein electrophoresis	£1.18	DAPS04	Clinical biochemistry	Directly accessed pathology services
Serum β2 microglobulin	£1.18	DAPS04	Clinical biochemistry	Directly accessed pathology services
C-reactive protein	£6.42	DAPS06	Immunology	Directly accessed pathology services
Serum erythropoietin level	£1.18	DAPS04	Clinical biochemistry	Directly accessed pathology services
Immunofixation	£6.42	DAPS06	Immunology	Directly accessed pathology services
Creatinine clearance	£1.18	DAPS04	Clinical biochemistry	Directly accessed pathology services
Routine urinalysis	£1.18	DAPS04	Clinical biochemistry	Directly accessed pathology services
24-hour urine measurement	£1.18	DAPS04	Clinical biochemistry	Directly accessed pathology services
24-hour urine for creatinine	£1.18	DAPS04	Clinical biochemistry	Directly accessed pathology services
Total urine protein	£1.18	DAPS04	Clinical biochemistry	Directly accessed pathology services
Urine protein electrophoresis/ light chains	£1.18	DAPS04	Clinical biochemistry	Directly accessed pathology services
Urine immunofixation	£6.42	DAPS06	Immunology	Directly accessed pathology services

Skeletal survey by X-ray	£181.56	DAPF	Direct access plain film (six sites assumed)	Directly accessed diagnostic services
Skeletal survey by X-ray individual sites	£30.26	DAPF	Direct access plain film	Directly accessed diagnostic services
Magnetic resonance imaging	£213.17	RA05Z	MRI scan, two or three areas, with contrast	Diagnostic imaging – outpatient
Bone densitometry	£70.71	RA15Z	Dexa scan	Diagnostic imaging – outpatient
Bone marrow aspirate	£266.83	SA33Z	Diagnostic bone marrow extraction	Procedures in outpatients – clinical haematology
Bone marrow trephine biopsy	£30.77	DAPS02	Histopathology and histology	Directly accessed pathology services
Bacterial investigation	£7.63	DAPS07	Microbiology	Directly accessed pathology services
Calcium	£1.18	DAPS04	Clinical biochemistry	Directly accessed pathology services
Albumin	£1.18	DAPS04	Clinical biochemistry	Directly accessed pathology services
Lactate dehydrogenase	£1.18	DAPS04	Clinical biochemistry	Directly accessed pathology services
RBC transfusion	£122.35	National Health Service (NHS). Blood and DTS pricing proposals for 2017/18.[128]		
Platelet transfusion	£178.19	National Health Service (NHS). Blood and DTS pricing proposals for 2017/18.[128]		

Key: MRI, magnetic resonance imaging; **RBC**, red blood cell; **NHS,** National Health Service.

B.3.5.5Subsequent treatment costs

The majority of patients (94%) receive subsequent lines of anti-myeloma treatment after experiencing progressive disease. Thus, OS and costs are influenced by the cumulative effects of multiple lines of treatment.

Costing of subsequent treatments in the model, and subsequent treatment disutilities for scenario analyses, were based upon the following data:

- Distribution of patients on treatments (based on the percentage of progressions being fatal, and probability of subsequent progression)
- Drug costs
- Duration of treatment

For simplicity, the model assumes subsequent treatment starts upon progression, however it is recognised in clinical practice that there may occasionally be a short delay between the progression assessment and intiation of subsequent treatment. Additionally, AE costs associated with each treatment were not included in post-progression cost estimations as these represent a very small proportion of incremental cost. However, costs of resource utilisation for disease monitoring (i.e. laboratory and monitoring tests) were calculated for patients in the 'progressive disease' state, independent of treatment. Rates of transfusion in the post-progression state were assumed to be the average of Rd, MPT and VMP.

The distribution of subsequent treatments is sourced from the MM-020 trial for Rd and MPT, and from the VISTA trial for VMP (Table 45) to avoid bias from a mismatch between subsequent treatment costs and the effectiveness data (i.e. OS) used in the economic model. This is in response to previous MM submissions which have come under criticisms from ERGs due to subsequent treatment costs not matching the effectiveness data used in the model.[56,129]

The subsequent treatment data from the MM-020 and VISTA trials provide comparable information on the number of patients on lenalidomide-, bortezomib- or thalidomide-based therapies. Calculations are therefore based on the cycle costs for lenalidomide, bortezomib and thalidomide only, multiplied by the associated mean number of cycles (Table 45).

Scenario analysis is provided to test the model sensitivity to subsequent treatment assumptions (cost of subsequent treatments removed plus subsequent treatment and OS assumed equal between VMP and MPT).

B.3.5.5.1 Distribution of patients on treatment

Time from first to second progression (Table 43) was taken from the MM-020 CSR for Rd and MPT.[43] There was a lack of data on VMP for these two inputs and, as such, the base case assumes equivalence to MPT given this is the reference treatment for the HR for OS for VMP; note this is likely biased in favour of VMP as a shorter time to second-line progression would be expected based upon the shorter OS seen for VMP versus MPT from the NMA. Patients in subsequent lines of therapy are calculated as follows:

- The difference in progression-free patients between cycles is multiplied by 1 minus the fatal progression rate (Table 43) to give the number of newly progressed patients moving into second-line; this is used to calculate the cost of second-line therapy.
- The number of newly progressed patients is added to the number of second-line patients from the previous cycle multiplied by 1 minus the calculated cycle probability of second progression or death (Table 43) to determine the number of patients remaining between first and second progression – this is used to calculate the number of patients remaining at second-line, and those receiving a post-progression disutility if selected in scenario analysis.
- The number of patients entering third-line is calculated by multiplying the number of patients remaining in second-line in the previous cycle by the cycle probability of progression, and 1 minus the second-line fatal progression rate, taken from Stadtmauer et al.[130] (17.5% for Rd, with MPT and VMP assumed equal). This is used to calculate the cost of third-line subsequent therapy.
- Those remaining in third-line or beyond are calculated as the number of progressed patients minus the number of patients remaining in second-line, and is used to calculate the disutility of third-line and beyond, if subsequent treatment disutilities are chosen.

Table 43: Subsequent treatment time inputs

	1L fatal progression rate* from MM-020	Time from 1st to 2nd progression (months)	Time from 1st to 2nd progression (cycles)	Rate of progression (per cycle)	Cycle probability of 2nd progression
Rd	23.1%	16.9	18.4	0.053	0.052
MPT	25.9%	13.1	14.2	0.068	0.066
VMP	25.9%	13.1	14.2	0.068	0.066

Key: 1L, first line; **MPT,** melphalan, prednisone and thalidomide; **MSM,** multi-state Markov; **Rd,** lenalidomide and low-dose dexamethasone until disease progression; **VMP,** bortezomib, melphalan and prednisone.
Note: If before the 92-week cut-off values from the MM-020 trial as described are used. After this cut-off, the transitions from the MSM matrices are used: progression-free to death/(progression-free to death + progression-free to progressed).

B.3.5.5.2 Subsequent treatment drug costs

The costs of subsequent treatments are given below in Table 44. The weighted cost per cycle for bortezomib includes an administration cost, the calculation of which is explained below. For simplicity, subsequent therapy costs are applied as a lump sum at the time of therapy initiation. This is likely to bias against treatments that progress and receive subsequent therapy later, when discounting would be higher.

The PAS for lenalidomide is also applied in subsequent lines. For the comparator arms, the existing cycle cap in which the cost of lenalidomide is capped at 26 cycles is applied in both second and third line despite NICE having only issued guidance (based on a 26-cycle cap) in third line. This assumes that if lenalidomide were to be given in second line in practice (as it was in the trial), the PAS would be applied.

In the intervention arm, the cycle cap proposed for this appraisal ([redacted] cycles) is used, based on the approach adopted by the ERG in the NICE appraisal of abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy (TA387).[131] The rationale being that the new PAS will only be operational, and hence applied in subsequent lines, if the intervention is recommended by NICE in this appraisal (based on a [redacted]-cycle cap).

For both the intervention and comparator arms, the cost of lenalidomide beyond the cycle cap is assumed to be zero. This is modelled through a decrease in the time on subsequent treatment.

The cost per cycle for bortezomib in second line also includes the relevant PAS. We have estimated the impact based upon the publicly available PAS details from NICE TA129.[132] The calculation has been undertaken as follows. Patients are assessed

after four cycles of treatment. If they achieve less than a partial response, they are refunded the costs of the drug that they incurred. Lee et al., 2008,[133] report that 92% and 69% in the bortezomib arm of the APEX trial completed at least two and four cycles, respectively. The primary reasons for discontinuation were progressive disease (29% of bortezomib arm), AEs (20%) and patient request (5%). We assume that the residual 46% discontinued because of stable disease. Considering the best responses reported by Richardson et al., 2005 (38% complete or partial response, 8% minor response),[134] this is reasonable. Thus 8% completed at most two cycles and 31% completed at most four cycles. Of those who discontinued, 75% did so because of progressive or stable disease. Therefore 8%*75% were eligible for rebate at two cycles and 31%*75% were eligible for rebate at four cycles. The impact of excluding this PAS has been tested in scenario analysis.

Table 44: Subsequent-line drug costs

Drug	Dose	Tx cycle length	No. doses per cycle	Cost per Package[a]	mg per pill/vial[a]	Pills/Vials per package[a]	RDI	Weighted cost per cycle
Lenalidomide	25 mg[b]	28[b]	21[b]	£4,368.00	25 mg	21	[redacted]	[redacted]
Bortezomib	1.3 mg/m[b c]	25[d]	4[c]	£762.38	3.5 mg	1	[redacted]	[redacted]
Thalidomide	200 mg[e]	28[e]	28[e]	£298.48	50 mg	28	71.6%[h]	£842.02

Key: kg, kilograms; **mg**, milligram; **No,** number; **Tx,** treatment.

[a], Source: MIMs, accessed Jan 2017.[125]

[redacted]

[c], Source: APEX – Richardson et al., 2005.[134]

[d], Average bortezomib cycle length in APEX: eight cycles of 21 days + three cycles of 35 days = 273 days/11 cycles = 25 days/cycle

[e], Source: Waage et al., 2010;[137]

[f] Assumption.

[g], Includes administration cost; [h], MM-010.[123]

B.3.5.5.3 Subsequent treatment use

Table 45 shows the duration of each subsequent therapy by line of treatment. As the treatments have different durations, costs are applied as a one-off upon initation of second- or third-line treatment. The duration of subsequent therapy is assumed not to be impacted by the treatment received in the 'progression-free' state. Duration of treatment for lenalidomide is adjusted for the PAS application, by assuming an exponential distribution for time on subsequent treatment as a simplification.

Table 45: Post-progression treatment durations

Treatment at each line	Source(s) of the data	Mean cycles used in model
Second line		
Lenalidomide-based therapy	MM-009 and MM-010 (no multiple prior relapses)[135,136]	[redacted]
Bortezomib-based therapy	APEX[134]	5.0
Thalidomide-based therapy	OPTIMUM[124]	7.0
Third line		
Lenalidomide-based therapy	MM-009 and MM-010 (no multiple prior relapses)[135,136]	[redacted]
Bortezomib-based therapy	APEX[134]	5.0
Thalidomide-based therapy	OPTIMUM[124]	7.0

Key: MPT, melphalan, prednisone and thalidomide; **NICE,** National Institute for Health and Care Excellence.

Table 46: Proportion of patients on subsequent therapy and total costs

1L	Received subsequent therapy	Therapy received			Source	Total costs
	2L	**Bort**	**Thal**	**Len**		
Rd	299	179	36	41	MM-020 CSR,[43] Table 42	[redacted]
MPT	381	170	25	150	MM-020 CSR,[43] Table 42	[redacted]
VMP	178	25	71	26	Mateos et al., 2010.[70]	[redacted]
	3L+	**Bort**	**Thal**	**Len**		
Rd	180	99	31	34	MM-020 CSR,[43] Salvage_reg34, d_pop survi2	[redacted]
MPT	231	133	13	130	MM-020 CSR,[43]Salvage_reg34, d_pop survi2	[redacted]
VMP	79	21	23	34	Mateos et al., 2010.[70]	[redacted]

Key: 1L, fist line; **2L,** second line; **3L,** third line**; CSR,** clinical study report; **MPT,** melphalan, prednisone and thalidomide; **Rd**, lenalidomide and dexamethasone until progression; **VMP,** bortezomib, melphalan and prednisone.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Table 47 summarises the variables and distributions applied in the economic model and references to the section in the submission where it is explained in more detail.

Table 47: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
HR for VMP versus MPT progression-free survival	1.00	CODA samples	Section B.2.9
HR for VMP versus MPT overall survival	1.11	CODA samples	Section B.2.9
MSM transition probabilities	Table 27	Bootstrapped samples	Section B.3.3
KM uncertainty	1	Normal distribution with SE of 0.13 (calibrated)	Section B.3.3
AE rates	Table 38	Beta distribution (MM-020 and VISTA)	Section B.3.5
Baseline utility	0.53	Beta distribution (SE from MM-020 patient-level data analysis)	Section B.3.4
Treatment and time coefficients/interactions for utility calculations	Table 29, Table 30	Multivariate normal distribution (variance/covariance from PLD analysis)	Section B.3.4
Resource use frequency	Table 40	Normal distribution (SE 15% of mean)	Section B.3.5
% of patients completing at most two and four cycles of Bort treatment	8% and 31%, respectively	Beta distribution (Lee et al. 2008)[133]	Table 44
% of patients on prophylactic aspirin	90%	Beta distribution (SE 15% of mean)	Table 36
% of patients requiring G-CSF annually	Rd and VMP, 18%; MPT, 35%	Beta distribution (MM-020)[43]	Table 36
Subsequent treatment RDI	Table 44	Normal distribution (SE 15% of mean)	Table 44
AE costs	Table 42	Normal distribution (SE	Table 42

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
		15% of mean)	
1L fatal progression probability (pre-cut off)*	Rd: 23.1%; MPT: 25.9%; VMP: 25.9%	Beta distribution (MM-020)[43]	Table 43
Time from first to second progression (months)	Rd: 16.9; MPT: 13.1; VMP: 13.1	Normal distribution (MM-020)	Table 43
Duration of subsequent treatment	Table 45	Normal distribution (SE 15% of mean)	Table 45

Key: CI, confidence interval; **HR,** hazard ratio; **RDI,** relative dose intensity.
Notes: *, uncertainty in fatal progression post-cut-off is captured in the MSM bootstraps.

B.3.6.2 Assumptions

Table 48 details the assumptions used in the economic model and provides a justification for each one. Section B.3.8.3 lists the assumptions that are varied in the scenario analysis.

Table 48: Base case assumptions

Assumption	Justification	Reference in submission
ITT populations of trials in the evidence network are representative of patients who are unable to tolerate or have contraindications to thalidomide	Based on the advice of clinical experts and the differences in toxicity profile and mechanism of action between thalidomide and lenalidomide, patients who present with predisposing conditions that make them more susceptible to thalidomide AEs may benefit from receiving Rd.	Section B.3.2
Progression and death are linked events that require modelling simultaneously	Rates of death from progression-free and progressed health states are different, with MSM reflecting the growing proportion of patients in the progressed health state influencing death rates	Section B.3.2
Relative efficacy between Rd and MPT changes after 92 weeks	Log-cumulative hazards of PFS for Rd and MPT arms diverge	Section B.3.3
Equal PPS between Rd and MPT after trial follow-up	The post-progression survival benefit expected from Rd is anticipated to be balanced by the subsequent use of Rd in the MPT arm	Section B.3.3
Proportional hazards between MPT and VMP	The time-varying HRs NMA results did not indicate a statistically significant time-dependency in the HRs for either PFS or OS.	Sections B.2.9 and B.3.3
Cycle hazards on each treatment are not lower than the general population	None of the modelled treatments are expected to provide overall survival benefits greater than that of the general population	Section B.3.3
Equal resource use post-progression	Simplifying assumption given none of the modelled treatments are expected to require substantial treatment-specific healthcare visits or assessments	Section B.3.5
AE rates for Rd and MPT change every 6 cycles, and are only applied in pre-progression	Patients likely to experience an AE will do so at the start of treatment, with serious AEs causing discontinuation, making them less frequent at later cycles. No modelled treatments are expected to cause AEs after treatment discontinuation and progression	Section B.3.5
AE-related disutility is captured in treatment covariate from utility analysis	Progression-free utility is calculated dependent on treatment, and it is expected that disutilities from AEs will be captured in the questionnaires completed by these patients	Section B.3.4
Utility status is dependent on time, treatment, age and progression	Analysis of EQ-5D data from MM-020 has indicated a significant effect of time and treatment on utility of ‘progression-free’.	Section B.3.4
Utility post-progression is equal between arms	None of the modelled treatments are expected to provide a post-progression utility benefit, with patient level data analysis not identifying any significant effect	Section B.3.4
[redacted]	[redacted]	Section B.3.5

Assumption	Justification	Reference in submission
Treatment duration for VMP is equal to PFS, up to the fixed number of cycles	This assumption has been made in the absence of data on time to treatment discontinuation for bortezomib, note as VMP is a fixed duration treatment assuming equivalence to PFS is reasonable given that clinicians will make every attempt to give the patient all doses even if delays to treatment are needed.	Section B.3.3
The maximum scheduled treatment duration for VMP (all patients on nine 42-day cycles) is used for modelling time on treatment, with no correction for progression or discontinuation from treatment, in the AG model in TA228	This is an interpretation based on reporting in the associated documentation for TA228, and is used to determine that the approach used in this analysis to estimate VMP treatment costs is more conservative than the assumption used in TA228 in the AG model.	Section B.3.3.5

AE, adverse event; **MPT,** melphalan, prednisone and thalidomide; **PPS,** post-progression; **PFS,** progression free survival; **Rd**, lenalidomide and dexamethasone until progression; **VMP,** bortezomib, melphalan and prednisone.

B.3.7 Base-case results

Two base-case analyses are presented:

- Rd vs. MPT, representing the analysis in the wider population of patients with NDMM for whom stem-cell transplantation is considered inappropriate. As described in Section B.3.2.1, a cost-effectiveness case cannot be made in this population due to thalidomide's low acquisition cost.
- Rd vs. VMP, in the subgroup of patients who are unable to tolerate, or have contraindications to thalidomide (in line with the final scope and TA228[3]). As described in Section B.3.2.1, this is the evaluation we ask the Committee to consider.

All results are presented based on the proposed PAS in which the cost of lenalidomide is capped at [redacted] cycles. Results based on the existing PAS in which the cost of lenalidomide is capped at 26 cycles are presented in Appendix P.

B.3.7.1 Base-case incremental cost-effectiveness analysis results

B.3.7.1.1 Rd vs. MPT

The base-case results for Rd versus MPT are shown in Table 49. Rd is associated with [redacted] incremental QALYs per patient, and an increase in overall costs of [redacted] per patient. The ICER is [redacted] per QALY gained.

Table 49: Base case results (with PAS) – vs MPT

Technologies	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER (per QALY)
MPT	[redacted]	[redacted]	[redacted]				
Rd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: MPT, melphalan plus prednisone plus thalidomide; **Rd,** lenalidomide low dose dexamethasone until disease progression; **LYs,** Life years; **QALY,** quality adjusted life year; **Inc.**, incremental

B.3.7.1.2 Rd vs. VMP in the subgroup of patients who are unable to tolerate or have contraindications to thalidomide

The base case results for Rd versus VMP are shown in Table 50. Rd is associated with [redacted] incremental QALYs per patient, and an increase in overall costs of [redacted] per patient. The ICER is [redacted] per QALY gained.

Table 50: Base case results (with PAS) – vs VMP in the subgroup of patients who are unable to tolerate or have contraindications to thalidomide

Technologies	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER (per QALY)
VMP	[redacted]	[redacted]	[redacted]				
Rd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: VMP, Bortezomib Melphalan Prednisone; **Rd,** lenalidomide low dose dexamethasone until disease progression; **LYs,** Life years; **QALY,** quality adjusted life year; **Inc.**, incremental

B.3.8 Sensitivity analyses

Sensitivty analyses for the comparison of Rd vs. MPT are not presented given a cost-effectiveness case cannot be made in this population due to thalidomide's low acquisition cost (Section B.3.2.1).

B.3.8.1 Probabilistic sensitivity analysis – Rd versus VMP

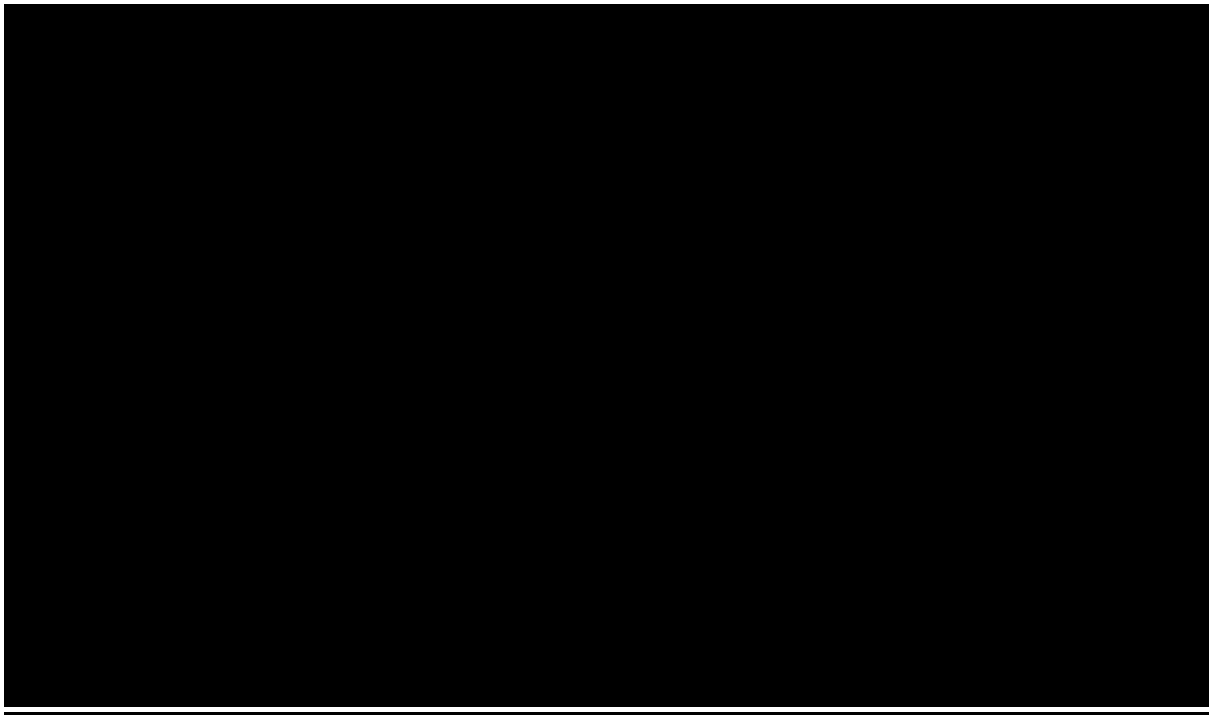
A PSA was performed by varying all inputs simultaneously over 1,000 iterations, based upon their distributional information (see Section B.3.6.1). The results are presented on a cost-effectiveness plane (Figure 24) and as cost-effectiveness acceptability curves (CEACs). Results from the PSA are presented below in Figure 24 and Table 51, with survival and QALYs contributing more uncertainty than costs.

Table 51: Probabilistic incremental cost-effectiveness analysis results (with PAS)

Technologies	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER (per QALY)
[redacted]	[redacted]	[redacted]	[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: VMP, Bortezomib Melphalan Prednisone; **Rd,** lenalidomide low dose dexamethasone until disease progression; **LYs,** Life years; **QALY,** quality adjusted life year; **Inc.**, incremental

Figure 24: Cost-effectiveness plane



Key: PSA, probabilistic sensitivity analysis; **QALY,** quality adjusted life year; **VMP,** bortezomib melphalan prednisone; **WTP,** willingness-to-pay.

Based on the CEAC (Figure 25) there is a [redacted] and [redacted] likelihood that Rd is cost-effective at willingness-to-pay thresholds of £20,000 and £30,000 per QALY respectively.

Figure 25: Cost-effectiveness acceptability curve

Key: **Rd,** lenalidomide and low dose dexamethasone until disease progression; **VMP,** bortezomib melphalan prednisone.

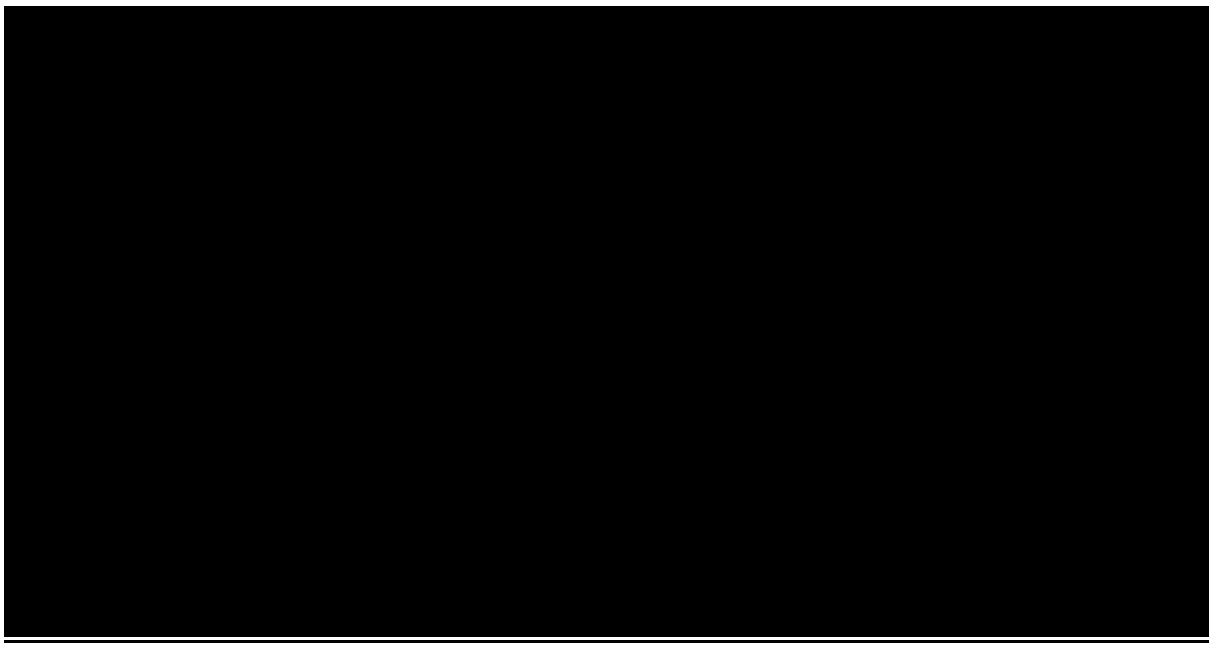
B.3.8.2 Deterministic sensitivity analysis – Rd versus VMP

A series of one-way sensitivity analyses (OWSA) were performed to evaluate the sensitivity of the model ICER to individual inputs, holding all else constant. In the deterministic sensitivity analysis, the lower and upper bounds of a parameter were often set to ± 1.96*SE of the base case value (or mean), where SE was obtained from its source data. Alternatively, confidence intervals were used where available. However, when such information was not available, the upper and lower bounds were assumed to be within ± 15% of the base case value. In a few cases, variation of a model parameter in deterministic sensitivity analysis was done per the NICE guidelines (e.g. 0% and 5% for discount rate).

All parameters described in Section B.3.6 are varied, aside from the MSM matrices which are only varied in the PSA due to their non-standard distribution.

Figure 26 presents a tornado diagram with parameters shown in descending order of ICER sensitivity.

Figure 26: Results of one-way sensitivity analysis – Rd vs. VMP



Key: DoT, duration of treatment; **HR,** hazard ratio; **MPT,** melphalan plus prednisone plus thalidomide; **OS,** overall survival; **Rd**, lenalidomide and low dose dexamethasone until disease progression; **TTF,** time to treatment failure; **VMP,** bortezomib melphalan prednisone.

The model is relatively insensitive to the majority of parameters, with no parameters other than the OS HR for VMP [redacted].

The parameters with the greatest impact on model outcomes were the HR for VMP overall survival, discount rate, parameters for time to treatment failure and utility inputs. However, the analysis varying the HR for VMP should be treated with caution as this fails to capture the correlation of this parameter with others in the model, such as subsequent therapy costs which would be associated with such variations in OS; this is addressed in the scenario analyses (Section B.3.8.3).

B.3.8.3 Scenario analysis – Rd versus VMP

The extensive range of scenarios tested are detailed in Table 52. The ICER is relatively insensitive to these analyses, with no scenarios [redacted]. Key results are as follows:

- Equal OS and subsequent therapy for VMP and MPT – assuming equivalent OS for VMP vs. MPT (based on the statistical insignificance of the HR estimated by the NMA) combined with the assumption of equivalent subsequent therapy use [redacted]. Given equal PFS was estimated by the NMA for VMP vs. MPT, variations in OS for VMP vs. MPT should be considered to result from the impact of variations in subsequent therapies on post-progression survival, hence this scenario is arguably more informative than the OWSA of the VMP HR for OS which fails to capture such correlation.
- Remove all subsequent treatment costs – setting all subsequent therapy costs to zero [redacted] per QALY gained.
- Equal PPS for Rd and MPT – the MSM analysis predicted a marginally lower per cycle probability of death from progressive disease for Rd vs. MPT (0.0194 vs. 0.0195 respectively). [redacted].
- Time-varying HRs for VMP and Rd vs. MPT – although the proportional hazards assumption was not violated for either Rd or MPT, the point estimates of the HR did show some potentially meaningful changes over time.

Relaxing the proportional hazards assumption for the period in which the HR was observed for each comparison [redacted]

- Remove treatment coefficient and interaction terms for utility calculations – these effects were not statistically significant however were included to capture the impact of treatment-related adverse events for Rd. [redacted]

Table 52: Scenario analyses – Rd versus VMP

Scenario and cross reference	Scenario detail	Brief rationale	ICER (vs. VMP)
Base case			[redacted]
Time horizon of 15 years	Alternative time horizons for the model	To observe the impact of the ICER on the model time horizon. This is impact minimal.	[redacted]
Time horizon of 35 years			[redacted]
Equal OS and subsequent therapy for VMP and MPT	VMP HR for OS and subsequent therapy proportions are set equal to MPT	To observe the impact of equal efficacy of VMP to MPT, which would be reflected with increased subsequent Rd use than reported in VISTA	[redacted]
Equal PPS for Rd and MPT	Set the MSM transition from PD to death equal for Rd and MPT	To observe impact of assuming no post-progression survival benefit for the Rd arm	[redacted]
Time-varying HRs for VMP vs. MPT	Use fractional polynomials to estimate the PFS and OS HR for VMP to MPT over time, using last HR carried forward at trial follow-up limit	To observe the impact of relaxing the proportional hazards assumption	[redacted]
Time-varying HRs for VMP and Rd vs. MPT	Use fractional polynomials to estimate the PFS and OS HR for VMP and Rd to MPT over time, using last HR carried forward at trial follow-up limit		[redacted]
Use TTF:PFS to extrapolate Rd and MPT DoT	Use the ratio of TTF to PFS from the Rd and MPT arms of the MM-020 trial, and apply to PFS to estimate DoT	An alternative method of estimated costs to parametric modelling of TTF from patient-level data from MM-020	[redacted]
Use Rd TTF:PFS for VMP DoT	Use the ratio of TTF to PFS from the Rd arms of the MM-020 trial, and apply to VMP PFS to estimate VMP DoT	In the absence of data, this scenario tests the impact of assuming Rd treatment discontinuation is applicable to the VMP arm	[redacted]
Assume VMP DoT from TA228	Remove the association of PFS with DoT for VMP, in line with the assumptions from TA228 – no treatment discontinuations, all	In the absence of data, this scenario tests the impact of assuming previous technology appraisal costings	[redacted]

	patients receive all 9 doses of VMP		
Use RDI for drug costs	[redacted]	An alternative method to estimate drugs costs to the trial-based dosing	[redacted]
VMP G-CSF equivalent to MPT	Assume equal G-CSF use between VMP and MPT	In the absence of data, this scenario estimates the impact of equal G-CSF use between VMP and MPT rather than Rd	[redacted]
Assume 100% VMP patients receive full rebate for bortezomib if achieving less than a partial response by the cut-off duration	Assume 100% patients receive full rebate if achieving less than a partial response by the cut-off duration	Explores the impact of assuming all patients receive the reimbursement, rather than 75%	[redacted]
Exclude bortezomib PAS	Set % of patients receive full rebate if achieving less than a partial response by the cut-off duration to zero	To observe the impact on the ICER of the bortezomib PAS (minimal)	[redacted]
Remove subsequent thalidomide costs	Set subsequent thalidomide costs to zero	To observe the impact on the ICER of subsequent thalidomide use given the subgroup explored is patients who are unable to tolerate, or have contraindications to thalidomide	[redacted]
Remove all subsequent treatment costs	Set all subsequent treatment costs to zero	To observe the impact on the ICER of subsequent treatment use	[redacted]
Include subsequent-treatment disutilities	Use subsequent treatment disutilities from Hatswell et al. to calculate post-progression utility	An alternative method of calculating post-progression utility	[redacted]
Remove treatment coefficient and interaction terms for utility calculations	Set treatment coefficient and interaction terms for utilities to zero	To observe the impact on the ICER of the treatment in utility calculations	[redacted]

Key: **DoT**, duration of treatment; **G-CSF**, granulocyte colony stimulating factor; **HR,** hazard ratio; **ICER;** incremental cost-effectiveness ratio**; MPT,** melphalan plus prednisone plus thalidomide; **OS,** overall survival; **PAS,** patient access scheme;, **PFS,** progression free survival; **PPS,** post-progression**; Rd,** lenalidomide and low dose dexamethasone until disease progression; **RDI,** relative dose intensity; **TTF,** time to treatment failure; **Rd**, lenalidomide and low dose dexamethasone until disease progression; **VMP,** bortezomib melphalan prednisone.

B.3.8.4 Summary of sensitivity analyses results

The analyses indicate the comparison between Rd and VMP is robust, [redacted]

Although OWSA identified the VMP OS HR as having the greatest impact on the ICER, the values used for the HR are the 95% credible intervals from the CODA samples, and the analyses assume no correlation between the associated change in OS for VMP and any other parameter. Thus, this analysis result should be interpreted with caution. When attempting to address this bias in the scenario analysis by assuming OS and subsequent therapy use were equal for VMP vs. MPT (in line with equality of PFS), Rd domainted VMP.

B.3.9 Subgroup analysis

Aside from the population of patients who are unable to tolerate or have contraindications to thalidomide, no other subgroups were considered in this submission.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Upon completion of programming, the model was validated by internal and external modellers. A programmer (other than the one who built the model) reviewed all formulas and labelling in the model. Following this first validation step, an extreme value analysis was conducted. This involved inputting sensible upper and lower bounds (e.g. £0 for costs, but not negative costs) into the model one parameter at a time and observing the corresponding changes in the results. Where it was not sensible to vary only one parameter or the expected effect on the results was not straightforward, a related group of parameters was varied simultaneously. The results were checked against their expected impact or the predicted direction of change for the varied parameter(s). For example, setting all AEs costs to zero would result in £0 for AE management across all treatment arms. The model was also validated and the modelling strategy and methodology critiqued by an academic health economist.

In addition, the predicted clinical outcomes were validated against studies identified by the SLR (Section B.3.1):

- Compared to the AG model developed for TA228, incremental LYs are a little different, with incremental LYs gained of [redacted] for MPT versus VMP, compared to 0.02 for MPT versus VMP in this cost-effectiveness model and TA228 submission, respectively. However, it is difficult to compare these two models as the HR used is against a different reference treatment, and the HR values themselves are marked CIC in the TA228 report.[3]
- Compared to Usmani 2016[97] (the only cost-effectiveness study identified by the SLR which compared Rd and VMP), incremental pre-progression LYs were similar ([redacted] in this cost-effectiveness model vs. 1.30). A more substantial difference was observed for post-progression LYs ([redacted] in this cost-effectiveness model vs. 1.94), however comparability of these studies is limited as they differer in the method used to extrapolate clinical outcomes, MM-020 data cut, discount rate for outcomes, and inclusion of Sacchi 2011 in the evidence network and consequently the HRs which inform relative effectiveness.

Predicted median PFS values from the model (Table 53) match well with the observed data on which the model was based. For example, the difference between the predicted and the trial reported median PFS for Rd was [redacted] months. The difference between the calculated median PFS for VMP (based on a HR for VMP vs. MPT from the NMA) and the reported value from the VISTA trial[39] [redacted]

Table 53: Median PFS (months), estimated in the model compared to reported values

Arm	Calculated by model	MM-020 trial	VISTA trial
Rd	[redacted]	26.0	–
VMP	[redacted]	–	24.0
MPT	[redacted]	21.9	-

Key: MPT, melphalan, prednisone and thalidomide; **PFS,** progression-free survival; **Rd,** lenalidomide and low-dose dexamethasone until disease progression; **VMP,** bortezomib, melphalan and prednisone.

Similarly, the OS estimates from the model are similar to those from the MM-020 trial (Table 54). The 4-year survival predictions from the model are equal to the trial data for Rd. Comparing median OS estimates, the model prediction for Rd ([redacted])

was [redacted] to that observed in the MM-020 trial (59.1 months). The predicted median OS for MPT was [redacted] of that observed in MM-020 (49.1 months).

Predicted median OS for VMP [redacted] than the observed median OS (56.4 months) from the VISTA trial. This is likely because the MPT arm of the MM-020 trial is used as the reference for the HR for OS for VMP and the study population in the VISTA trial seemed to be healthier compared to patients enrolled in the MM-020 trial, who are older (median age: 73 years versus 71 years) and sicker (ISS stage 3: 40% versus 35%).

Table 54: Four-year OS (%) and median OS (months), estimated in the model compared to reported values

Arm	Calculated by model		FIRST (MM-020) trial		VISTA trial
	4-year OS	Median OS	4-year OS	Median OS	Median OS
Rd	[redacted]	[redacted]	58.99%	59.1	–
VMP	[redacted]	[redacted]	–	–	56.4
MPT	[redacted]	[redacted]	51.67%	49.1	–

Key: MPT, melphalan, prednisone and thalidomide; **OS,** overall survival; **Rd,** lenalidomide and low-dose dexamethasone until disease progression; **VMP,** bortezomib, melphalan and prednisone.

B.3.11 Interpretation and conclusions of economic evidence

Despite the improvement in PFS and OS with the use of VMP and MPT in transplant-ineligible patients with NDMM, most patients relapse within about 2 years and experience a high rate of drug toxicities and poor HRQL. A clear unmet need still exists for this population as MM is characterised by regression and remission, and ultimately treatment failure, indicating the presence of residual disease even in patients who initially show a complete clinical response to treatment.[26] One of the principle advantages of Rd is that it can be given as continuous treatment based on its toxicity profile.[5] Rd treatment has been clearly shown to have long-term superior clinical benefits over MPT in the MM-020 trial and over VMP in the NMA.

The model uses the latest cut off (21 January 2016, median follow-up of 67 months) of patient-level data from the ITT population of the MM-020 study, and uses a structure that captures the key aspects of the disease regarding benefits and costs and reflects the most recent NICE DSU guidance on cancer modelling.[100]

This evaluation focuses on the cost-effectiveness of Rd vs. VMP in the subgroup of patients who are unable to tolerate or have contraindications to thalidomide, as a

cost-effectiveness case for cannot be made for Rd when compared against MPT due to thalidomide's low acquisition cost. Compared to VMP, this evaluation replicates the clinical benefits for Rd predicted by the NMA (i.e. prolonged PFS and OS), yielding incremental QALYs of [redacted]. This is predominantly driven by gains in the 'pre-progression' state stemming from the continuous nature of Rd. These benefits were accrued at reasonable additional costs [redacted]; [redacted]

This yields an ICER for Rd vs. VMP of [redacted] per QALY gained when the PAS is applied. The corresponding probability that Rd is cost-effective at a decision threshold of £30,000 per QALY is [redacted]. Moreover, the ICER was insensitive to OWSA and a range of scenario analyses exploring key assumptions. Adopting a HR for OS for VMP of 0.82 (lower 95% credible interval from NMA) [redacted], however this may be subject to bias as previously described, and hence should be interpreted with caution. Analyses attempting to correct this bias reinforced the cost-effectiveness of Rd.

In conclusion, these results indicate Rd is a cost-effective use of NHS resources in patients who are unable to tolerate or have contraindications to thalidomide, and should be recommended for this patient population to help to address the unmet medical need faced by these patients.

Key limitations include the lack of maturity of HRQL data where few observations are available post progression (although again scenarios using external literature show that the base case which uses only the trial data presents a conservative estimate of the ICER) and a lack of data for VMP for some parameters necessitating the use of assumptions based upon data for Rd and MPT.

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Single technology appraisal

Lenalidomide in combination with dexamethasone for previously untreated multiple myeloma [ID474]

Dear Company,

The Evidence Review Group, Southampton Health Technology Assessments Centre, and the technical team at NICE have looked at the submission received on 25 October from Celgene. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by the end of **27 November 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as [redacted] in turquoise, and all information submitted as [redacted] in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Thomas Strong, Technical Lead (thomas.strong@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (jeremy.powell@nice.org.uk).

Yours sincerely

Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

FIRST trial (MM-020)

A1. Please provide details of the use of concomitant therapy during the active treatment phase for the MM-020 trial for all randomised groups, as details reported in Table 9 (page 29, Document B) are for the continuous lenalidomide group only (safety population).

A2. Page 33 of Document B states that all patients received protocol-specified antithrombotic prophylaxis. The supplementary appendix of the Benboubker New England Journal of Medicine paper states that patients could, after 4 months, switch to low-dose aspirin at the investigator's discretion. How many patients switched to aspirin?

A3. We note a discrepancy in the statistical power calculation for the primary endpoint of PFS between the company submission and the trial journal publication. There is a difference in the expected hazard ratio, as underlined below.

In B.2.4.1 it states: "*A total of approximately 1,590 patients (530 in each arm) were enrolled, with accrual of about 67 patients per month for 24 months. With a 24-month accrual period and 36-month follow-up after the study closed to accrual, a sample size of 530 patients in each treatment arm would have 80% power to detect a hazard rate ratio of 1.25 using a 2-sided log-rank test with an overall significance level of 0.05.*"

In the journal publication it states: "*We estimated that 1590 patients (530 per treatment group) would need to be enrolled to provide the study with 80% power to detect a hazard ratio of 0.80 for disease progression or death (continuous lenalidomide–dexamethasone vs. MPT), using a two-sided log-rank test with a significance level of 0.05, including one interim analysis".*

We also note there is inconsistency in these hazard ratios in the trial protocol (appended to the journal article) on pages 350 and page 391.

Could you explain the discrepancy?

A4. On page 41 of Document B it states that: "*given that the Rd and Rd18 arms were identical during this interval, HRQoL data for these two arms were pooled*". Please present HRQoL results separately for the Rd and Rd18 groups in order for us to assess if there were any differences between the groups.

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A5. Please provide references to any key publications describing the development and use of the EORTC QLQ-MY20 instrument. Specifically, has it been validated?

A6. An efficacy evaluable population is mentioned in Document B page 38, defined as *"The efficacy-evaluable population was defined as ITT patients who met protocol requirements (either met eligibility criteria and/or had measurable disease at baseline) and were evaluated after receiving at least one dose of study treatment".* Please clarify whether any of the results for this population are presented in the submission or used in the economic model.

A7. The submission states that there were 906 deaths across the treatment groups at the January 2016 data cut-off (B.2.6.4, page 52). However, the number of reported death by treatment group (page 78, Document B) equates to 903 patients (284+336+283). Could you explain the discrepancy?

A8. In Figure 32 in Appendix D.1.2 under the discontinued study heading, there is a group called 'other', which includes 130 patients across treatment groups. Please explain what 'other' refers to.

A9. Please provide results, including hazard ratio (HR) with confidence intervals, median progression-free survival (PFS) and Kaplan–Meier survival curve, for the investigator assessment of PFS at the May 2013 cut-off, to allow comparison with the Independent Response Adjudication Committee (IRAC) assessment of PFS at that time.

Network meta-analysis (NMA)

A10. Please clarify if any pairwise meta-analysis was conducted for head-to-head comparisons of MPT vs MP. If so, please state whether the results were consistent with those of this comparison in the NMA, and whether there was statistical heterogeneity.

A11. Please clarify what the dashed lines are in Figures 15 and 16 (page 68 and 70, Document B) – are these credible intervals around the respective hazard ratios (straight lines)?

A12. On page 68 of Document B, with reference to the time-varying HRs for overall survival (OS), it is stated that the HR of Rd relative to MPT becomes "statistically significant at approximately 20 months". Likewise, on page 70 with reference to the time-varying HRs for PFS it is stated that the HR of Rd relative to MPT decreases over time with the difference becoming "statistically important at approximately 18 months". Please clarify what is meant by this, and how this was measured/quantified.

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A13. Please supply interpretation of the data in Tables 19 and 21 (page 69-71, Document B). For example, what does the size of the correlation values signify in terms of the goodness of the model fit?

A14. **Priority question:** Please elaborate on the choice of fractional polynomial model for OS and PFS as shown in Table 10 and Table 11 in Appendix D (page 37 to 38). It appears that the model with the lowest Deviance Information Criterion (DIC) value was chosen, but were any other considerations taken into account in the choice of model fit? (E.g. the clinical plausibility of the model chosen with respect to PFS and OS curves as observed in the trials).

A15. **Priority question**. Please supply the NMA results for OS and PFS for each of the other 5 fractional polynomial parametric survival models in Table 10 and Table 11 (Appendix D). Please provide these results in the same format as used in the main company submission document (e.g. Figures 15 and 16 and Tables 19 and 21). This will enable us to compare variation in HRs between different order models. In addition, please supply zero-order fractional polynomial results for OS and PFS. As we understand it, this corresponds to a proportional hazards estimation and will enable us to assess comparability with the constant HR NMA. Please provide updated base-case cost-effectiveness results based on each of these analyses.

A16. Please supply heterogeneity statistics for the fixed-effect constant HRs NMAs presented in section B.2.9.

A17. **Priority question:** We acknowledge the statement that a fixed-effect NMA was done rather than a random-effects NMA due to the sparseness of the network, and the wide credible intervals for the heterogeneity parameter (as stated in Appendix D.1.1.5, page 35). For transparency and comparison purposes please supply the random effects constant HRs NMA results for both OS and PFS.

A18. Table 13 in Appendix D.1.3 contains a quality assessment for Facon 2006 (IFM-95/01). However, this trial also appears in Table 59 of Appendix D, which lists excluded studies. Please confirm whether or not this trial should have been quality assessed as an included study.

Section B: Clarification on cost-effectiveness data

B1. On page 101, Document B, it is stated that patients who died or were censored for OS prior to 92 weeks were not included in the MSM analysis. Please state how many patients this applied to.

B2. The weighted costs per model cycle shown in Table 36, Document B, differs from the values in the economic model in worksheet Drug Costs. Please clarify which values are correct.

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B3. The pack cost reported for melphalan and prednisolone in Table 35, Document B, differs from those reported in the economic model in worksheet Drug Costs. Please confirm which values are correct.

B4. **Priority question:** Please provide a mapping of EORTC QLQ C30 data for the Rd and MPT groups to EQ-5D values for cycles 1-6 using the mapping algorithm by Proskorovsky et al.

B5. **Priority question**: The submission provides a scenario analysis of VMP vs. Rd using time-varying HRs using fractional polynomials (Table 52, Document B). Please conduct a one-way sensitivity analysis for this analysis using the upper and lower 95% credible interval values.

B6. **Priority question:** Please clarify how you obtained the cost-effectiveness results for the scenario analysis: "Use TTP:PFS to extrapolate Rd and MPT DoT" (Table 52, Document B). Currently, choosing the option of "TTP:PFS" from the drop down menu in cell "DoT.Choice" within **Sheet!TTF and KMs** in the Excel model gives an error in the cost-effectiveness results"

Section C: Textual clarifications and additional points

C1. The clinical study report for the FIRST trial (reference 43 in the submission) contains table headings in section 14, but there are no tables provided. Please supply these.

C2. Figure 21 (page 106, Document B), PFS (left hand panel) – should an MPT survival curve appear in this figure?

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Lenalidomide in combination with dexamethasone for previously untreated multiple myeloma (ID474)

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Yours sincerely

Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

Section A: Clarification on effectiveness data

FIRST trial (MM-020)

A1. Please provide details of the use of concomitant therapy during the active treatment phase for the MM-020 trial for all randomised groups, as details reported in Table 9 (page 29, Document B) are for the continuous lenalidomide group only (safety population).

Use of concomitant therapy during the active treatment phase in the safety population are presented for all randomised groups in Table 1.

Table 1: Use of concomitant therapy during the active treatment phase in the safety population

Category	Rd N = 532	Rd18 N = 540	MPT N = 541
Antithrombotic, n (%)	531 (99.8)	539 (99.8)	534 (98.7)
Heparin, n (%)	48 (9.0)	17 (3.1)	17 (3.1)
Warfarin, n (%)	32 (6.0)	15 (2.8)	17 (3.1)
Anti-infective, n (%)	430 (80.8)	412 (76.3)	363 (67.1)
Erythropoietin stimulating agent, n (%)	160 (30.0)	150 (27.8)	162 (29.9)
Granulocyte-colony stimulating factor, n (%)	93 (17.5)	93 (17.2)	188 (34.8)

Key: Rd, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide.
Source: Clinical Study Report CC-5013-MM-020/IFM 07-01.[1]

A2. Page 33 of Document B states that all patients received protocol-specified antithrombotic prophylaxis. The supplementary appendix of the Benboubker New England Journal of Medicine paper states that patients could, after 4 months, switch to low-dose aspirin at the investigator's discretion. How many patients switched to aspirin?

We can confirm that subjects with a medical history of deep vein thrombosis (DVT) or pulmonary embolism (PE) within 5 years of randomisation received either a prophylactic dose of anticoagulation therapy with low molecular weight heparin (LMWH) or heparin (at a dose recommended for prophylaxis of DVT/PE per the package insert) or warfarin (Coumadin®; per the therapeutic index recommendations for DVT/PE to maintain an international normalised ratio [INR] of 2.0 to 3.0) for at least the first 4 months (16 weeks) of study participation.

Then, at the discretion of the treating physician, oral low-dose aspirin (70 to 100 mg daily) or continued anticoagulation therapy was given to these subjects for the remainder of the study. The number of patients who switched to aspirin in each study arm is reported in Table 2.

Table 2: Aspirin use in patients switching from antithrombotic prophylaxis

Category	Rd N = 532	Rd18 N = 540	MPT N = 541
Patients who received a prophylactic dose of anticoagulation therapy with low molecular weight heparin, heparin or warfarin, n (%)	12 (2.3)	10 (1.9)	11 (2.0)
Patients who switched to aspirin, n (%)	2 (0.4)	2 (0.4)	1 (0.2)

Key: Rd, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide.
Source: Clinical Study Report CC-5013-MM-020/IFM 07-01.[1]

A3. We note a discrepancy in the statistical power calculation for the primary endpoint of PFS between the company submission and the trial journal publication. There is a difference in the expected hazard ratio, as underlined below.

In B.2.4.1 it states: "*A total of approximately 1,590 patients (530 in each arm) were enrolled, with accrual of about 67 patients per month for 24 months. With a 24-month accrual period and 36-month follow-up after the study closed to accrual, a sample size of 530 patients in each treatment arm would have 80% power to detect a hazard rate ratio of 1.25 using a 2-sided log-rank test with an overall significance level of 0.05*."

In the journal publication it states: "*We estimated that 1590 patients (530 per treatment group) would need to be enrolled to provide the study with 80% power to detect a hazard ratio of 0.80 for disease progression or death (continuous lenalidomide–dexamethasone vs. MPT), using a two-sided log-rank test with a significance level of 0.05, including one interim analysis".*

We also note there is inconsistency in these hazard ratios in the trial protocol (appended to the journal article) on pages 350 and page 391.

Could you explain the discrepancy?

The hazard ratio in the protocol for an expected power of 0.80 was presented with reference to the melphalan in combination with prednisone and thalidomide (MPT)-arm hazard:

$$\frac{\lambda_{Rd}}{\lambda_{MPT}} = \frac{\{\text{Median survival of MPT}\}}{\{\text{Median survival of Rd}\}} = \frac{24}{30} = 0.8$$

In contrast, the hazard ratio in the journal publication was presented with reference to the lenalidomide and low-dose dexamethasone until disease progression (Rd)-arm hazard:

$$\frac{\lambda_{MPT}}{\lambda_{RD}} = \frac{30}{24} = 1.25$$

The company apologises for the lack of clarity regarding these data.

A4. On page 41 of Document B it states that: "*given that the Rd and Rd18 arms were identical during this interval, HRQoL data for these two arms were pooled*". Please present HRQoL results separately for the Rd and Rd18 groups in order for us to assess if there were any differences between the groups.

Please see Appendix 1 of the clarification response (the contents of which are academic in confidence [AIC]) which presents health-related quality of life (HRQoL) results for each treatment group based on European organisation for research and treatment of cancer core quality of life questionnaire (EORTC QLQ-C30), EORTC multiple myeloma module (EORTC QLQ-MY20) and EuroQol-5D (EQ-5D).

A5. Please provide references to any key publications describing the development and use of the EORTC QLQ-MY20 instrument. Specifically, has it been validated?

We can confirm that the EORTC QLQ-MY20 instrument has been validated. The relevant publication is:

Cocks K, Cohen D, Wisløff F, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-MY20) in assessing the quality of life of patients with multiple myeloma. *Eur J Cancer*. 2007;43(11):1670-1678.

The corresponding full text publication[2] has been included in the reference pack for the clarification responses.

A6. An efficacy evaluable population is mentioned in Document B page 38, defined as *"The efficacy-evaluable population was defined as ITT patients who met protocol requirements (either met eligibility criteria and/or had measurable disease at baseline) and were evaluated after receiving at least one dose of study treatment".* Please clarify whether any of the results for this population are presented in the submission or used in the economic model.

We can confirm that results for the population used in the efficacy section of the submission and the economic model are based on the intention-to-treat (ITT) population (n=1623). The efficacy-evaluable population was a secondary population for the efficacy analyses which was not used.

The submission also refers to the safety population which was defined as all randomised patients who received at least one dose of the study treatment (n=1,613). Data from the safety population is presented in the adverse reactions section of the submission (B.2.10).

A7. The submission states that there were 906 deaths across the treatment groups at the January 2016 data cut-off (B.2.6.4, page 52). However, the number of reported death by treatment group (page 78, Document B) equates to 903 patients (284+336+283). Could you explain the discrepancy?

We can confirm that there is no discrepancy here and that the information on both pages of the original company submission are correct. The difference in deaths reported can be explained by the difference in the patient population being considered.

- The figures on page 52 of the submission (B.2.6.4) are based on the intent to treat (ITT) population which was defined as all patients who were randomised, independent of whether they received study treatment. In total, 1,623 patients were enrolled and randomised in a 1:1:1 ratio to Rd (n = 535), Rd18 (n = 541) or MPT (n = 547).

- The figures on page 78 of the submission (the safety section) are based on the safety population which was defined as all randomised patients who received at least one dose of the study treatment. Here data for 1,613 patients who received at least one dose of any study drug were included.

As stated in answer to question A6, we can confirm that efficacy results for the population used in the economic model are based on the *ITT* population.

A8. In Figure 32 in Appendix D.1.2 under the discontinued study heading, there is a group called ‘other’, which includes 130 patients across treatment groups. Please explain what ‘other’ refers to.

Table 3 provides the full text descriptions of the reasons for study discontinuation for the 130 patients whose reason for discontinuing the study was listed as ‘other’ in the CONSORT diagram. Due to reporting of these data, there may be categories which are replicated due to spelling and added specifics.

Table 3: Study discontinuations

Reason	Count
AE #28 AND #29	1
BASED ON PRINCIPAL INVESTIGATOR'S DECISION	1
BEGIN NEW ANTIMYELOMA THERAPY	1
CHOOSE OF THE PATIENT, PT WITHDREW CONSENT FROM ACTIVE TRT BUT AGREED TO BE FOLLOWED IN LONG TERM FOLLOW UP	1
CLINICAL DETERIORATION NOT RELATED TO MYELOMA OR TREATMENT	1
DETERIORATION OF COGNITIVE IMPAIRMENT	1
DIFFICULT FOLLOWING UP WITH SUBJECT	1
DISEASE PROGRESSION BASED ON LOCAL LABS	1
DOCTOR STARTED PT ON A NEW MM DISEASE.	1
DUE TO SECOND PRIMARY MALIGNANCY	1
FAMILY'S DECISION	1
FOR STARTING CHEMOTHERAPY	1
INABILITY TO COMPLY WITH PROTOCOL	1
INCREASED IN FREE LIGHT CHAIN	1
INTOLERANCE OF TREATMENT	1
INVESTIGATOR AND PATIENT DECISION	1
INVESTIGATOR DECISION	6
INVESTIGATOR DECISION , DISEASE PROGRESSION WITH LOCAL RESULTS	1
INVESTIGATOR DECISION DUE TO EVOLVING LESION OF RIGHT COSTOVERTEBRAL ANGLE OF THE SEVENTH THORACIC VERTEBRA	1
INVESTIGATOR DECISION LACK OF RESPONSE	1
INVESTIGATOR DECISION,STEROIDS TO BE GIVEN OFF PROTOCOL	1
INVESTIGATOR DECISION	1
INVESTIGATORS DECISION	2
INVESTIGATOR'S DECISION	1
INVESTIGATORS DECISION - PROGRESSIVE DISEASE - BASED ON CLINICAL SIGNS AND SYMPTOMS	1

INVESTIGATORS DECISION, TREATMENT RESISTANT, RADIATION THERAY WAS PLANNED	1
INVESTIGATOR'S DECISION'S	1
JUDGMENT BIAS ON ZMWG CRITERIA	2
LACK OF EFFICACY IN VIEW OF TOXICITY	1
LIGHT CHAIN ESCAPE	1
LOCAL LAB'S RESULTS SHOWS PD	1
MEDICAL DECISION	5
MEDICAL DECISION STILL STABLE AFTER 9 CYCLES	1
MEDICAL MONITOR DECISION	1
MISTAKENLY DISCONTINUED FOR PD	1
MOVING TO ANOTHER CITY	1
NEW TREATMENT STARTED	1
NON COMPLIANCE	1
NON COMPLIENCE BY PATIENT	1
NON-COMPLIANCE	1
PATIENT CHOICE	1
PATIENT DECISION	5
PATIENT DECISION TO STOP STUDY MEDICATION	1
PATIENT DECISION TO STOP TREATMENT	1
PATIENT DID NOT ATTEND DISCON VISIT DUE TO LONG TRAVEL DISTANCE, WISHES TO STOP PFS VISITS	1
PATIENT DID NOT WISH TO CONTINUE WITHE THE STUDY AND WITHDREW CONSENT TO FURTHER RX BUT WAS HAPPY TO GON INTO LONG TERM FOLLOW UP	1
PATIENT HAS CHOOSEN ANOTHER TREATMENT PLAN	1
PATIENT IS NOT WILLING TO TRAVEL EVERY MONTH, WANTS TO BE FOLLOWED CLOSE TO HOME.	1
PATIENT IS UNABLE TO FOLLOW THE STUDY PROCEDURES	1
PATIENT MUST GO 2 MONTH ON VACATION IN WEST INDIES: DECISION OF INVESTIGATOR	1
PATIENT REFUSED CONTINUING MONTHLY PFS VISITS	1
PATIENT REFUSED FURTHER MONTHLY PFS	1
PATIENT REFUSED FURTHER PFS VISITS DUE TO IMMEDIATE TREATMENT NEED FOR BLADDER CANCER	1

PATIENT REFUSED FURTHER TREATMENT	1
PATIENT REFUSED PFS FOLLOW-UP	1
PATIENT TRAVELLING OVERSEAS AND DID NOT WISH TO ATTEND RGULAR PFS VISITS.	1
PATIENT UNABLE TO ATTEND APPTS, BUT AGREED TO PARTICIPATE IN LONG TERM FOLLOW UP.	1
PATIENT UNABLE TO PRESENT REGULARLY FOR PFS VISITS. NOW INTO LTFU	1
PATIENT WANT TO LEAVE THE STUDY	1
PATIENT WANT TO STOP STUDY DRUG	1
PATIENT WANTS TO LEAVE THE STUDY	1
PATIENT WHO MOVED	1
PATIENT WISHED DISCONTINUATION	1
PATIENT WISHED TO COMPLETE PFS AND ENTER LTFU	1
PATIENT WISHED TO DISCONTINUE FROM ACTIVE TREATMENT HOWEVER AGREED ON LETTING US COLLECT LONG TERM FOLLOW UP DATA.	1
PATIENT WITH DREW CONSENT TO ACTIVE TREATMENT BUT AGREED TO PHONE CALLS AND CHART REVIEW	1
PATIENT WITHDREW CONSENT BUT AGREED TO BE FOLLOWED IN LT-UP	1
PATIENT WITHDREW CONSENT FROM ACTIVE TREAMENT BUT AGREED TO PHONE CALLS AND CHART REVIEWS	1
PATIENT WITHDREW CONSENT FROM ACTIVE TREATMENT AND MOVED TO LTFU	1
'PATIENT WITHDREW CONSENT ONLY FOR FURTHER TREATMENT IN THE STUDY	1
PATIENT´S FAMILY DECISION	1
PATIENT'S DECISION	2
PATIENT'S DECISION FOR DISCONTINUATION	1
PATIENT'S REFUSAL	1
PD ACCORDING TO LOCAL LABS AND PI'S DECISION TO ENTER PATIENT IN ANOTHER TRIAL	1
PER SUB-INVESTIGATOR'S DISCRETION - ELEVATED FLCS	1
PHYSICIAN DECISION	1
PHYSICIAN DISCRETION	1
PHYSICIAN DISCRETION - AGE RELATED CONDITIONS ARE WORSENING	1
PHYSICIAN`S DECISION	1
PHYSICIANS DECISION	1

PI DECISION	2
PI DECISION TO DISCONTINUE PATIENT FROM STUDY.	1
PI DISCREATION	2
PI'S DISCRETION	1
PLASMAPHERESIS (PROCEDURE)	1
POOR GENERAL CONDITION	1
POOR PATIENT COMPLIANCE	1
POOR TOLERANCE TO THERAPY	1
PRINCIPAL INVESTIGATOR DECISION	1
PRINCIPAL INVESTIGATORS DISCRETION	1
PROGRESSIVE DISEASE ASSESSED IN ERROR FROM RADIOLOGY REPORTS. PATIENT SHOULD NOT HAVE BEEN DISCONTINNUED.	1
PROTOCOL INCOMPLIENCE DUE TO WORSENING ILLNESS	1
STARTED NEW ANTI MM THERAPY BY SUBJECT'S REQUIREMENT ,SUBJECT HIMESELF WANT TO USE OTHER TREATMENT FOR THIS DISEASE	1
SUBI PULLED HIM OFF STUDY BASED ON FREE LIGHT CHAIN LOCAL LABS	1
SUBJECT DECIDED TO WITHDRAW STUDY TREATMENT.	1
SUBJECT DID NOT WANT TO COME TO THIS CENTRE ANY MORE; PER SOURCE, SUBJECT ' IS IN AGREEMENT WITH US FOLLOWING HIS PROGRESS THROUGH MONITORING HIS CHART OR CALLING HIM OR HIS DOCTORS'	1
SUBJECT IS TOO ILL TO RETURN TO CLINIC	1
SUBJECT REFUSE TO CONTINUE STUDY TREATMENT	1
SUBJECT RELOCATED TO ANOTHER PROVINCE AND WITHDREW CONSENT, THEREFORE DISCONTINUED FROM THE STUDY.	1
SUBJECT REQUIRED TO CHANGE TREATMENT	1
SUBJECT WANTS TO MOVE INTO LONG-TERM FOLLOW-UP	1
SUBJECT WITHDREW CONSENT FROM ACTIVE TREATNT AND HAS DECLINE PARTICIPATION FOR PFS PHASE, BUT HAS AGREED TO BE FOLLOWED FOR OVERAL SURVIVAL (LTFU).	1
THE PAYIENT QUIT THE TRIAL AND REFUSE TO COME TO HOSPITAL FOR EXAMINATON,BUT HE STILL BEEN FOLLOWED UP	1
THERAPY CONVERSION	1
THIS PATIENT REFUSED TO CONTINUE TO PARTICIPATE IN STUDY	1
THIS PATIENT WITHDREW CONSENT ONLY FOR STUDY DRUG NOT FOR LONG TERM FOLLOW UP	1

TOO LONG TREATMENT PAUSE DUE TO PLANNED SURGERY	1
TREATMENT INTOLERANCE	1
UNCONFIRMED PD	1
UNSATISFACTORA THERAPEUTIC EFFECT (STABLE DISEASE) AFTER 6 MONTH OF THERAPY	1
WITHDREW PARCIAL CONSENT AS WAS HAPPY TO BE FOLLOW-UP FOR SURVIVAL WITHOUT ANY PROCEDURAL INTERVENTIONS	1

A9. Please provide results, including hazard ratio (HR) with confidence intervals, median progression-free survival (PFS) and Kaplan–Meier survival curve, for the investigator assessment of PFS at the May 2013 cut-off, to allow comparison with the Independent Response Adjudication Committee (IRAC) assessment of PFS at that time.

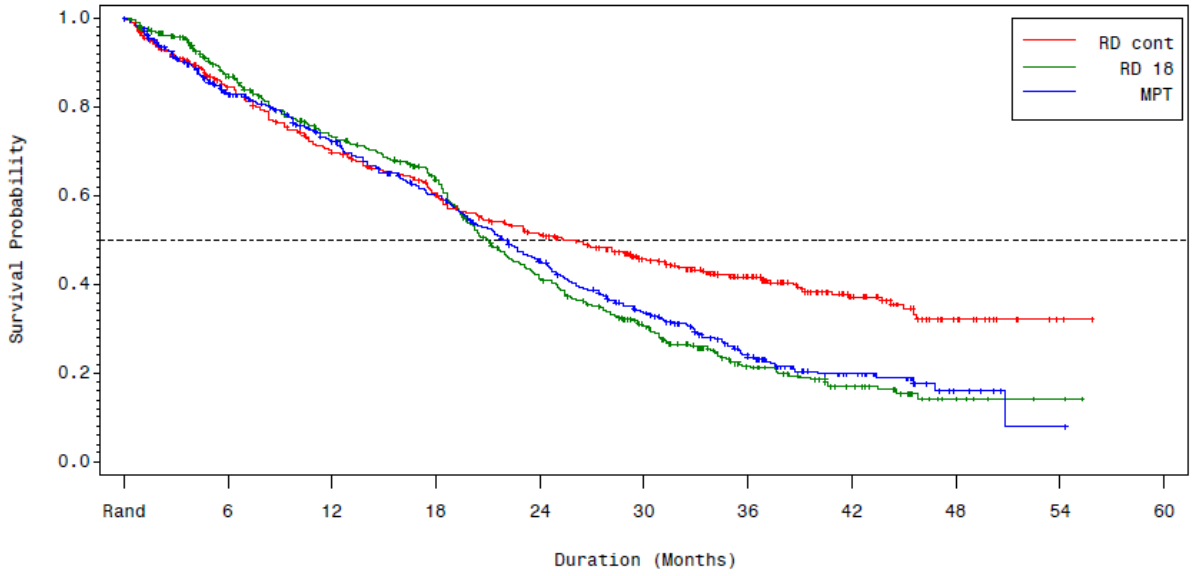
Results for PFS per the investigator assessment at the May 2013 cut-off using International Myeloma Working Group (IMWG) criteria are presented based on Food and Drug Administration (FDA) criteria (Table 4 and Figure 1). All results are for the ITT population.

Table 4: Progression free survival (PFS) results per investigator assessment using IMWG criteria in the ITT population (FDA censoring criteria), 24 May 2013 data cut-off

	Rd (n = 535)	**Rd18 (n = 541)**	**MPT (n = 547)**
PFS events, n (%)			
Censored	251 (46.9)	189 (34.9)	215 (39.3)
Died	53 (9.9)	40 (7.4)	50 (9.1)
PFS, months			
Median[a]	26.0	21.0	21.9
Comparison	**Rd vs MPT**	**Rd vs Rd18**	**Rd18 vs MPT**
HR (95% CI)[b]	0.74 (0.63–0.87)	0.72 (0.61–0.84)	1.04 (0.89–1.20)
Log-rank test *p* value[c]	0.0002	0.00003	0.64378

Key: Rd, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **HR**, hazard ratio
Note: Treatment Rd vs. MPT is the primary analysis. CI=Confidence interval. NE = Not Estimable.
[a] The median is based on Kaplan-Meier estimate.
[b] Based on unstratified Cox proportional hazards model.
[c] The p-value is based on unstratified log-rank test.

Figure 1: Kaplan-Meier plot of progression free survival (PFS) per investigator assessment using IMWG criteria in the ITT population (FDA censoring criteria), 24 May 2013 data cut-off



SUMMARY:

Group	N	Event	Censored	Median
RD cont	535	284(53.1%)	251(46.9%)	26.0
RD 18	541	352(65.1%)	189(34.9%)	21.0
MPT	547	332(60.7%)	215(39.3%)	21.9

Number at Risk:

Group	0 Months	6 Months	12 Months	18 Months	36 Months	54 Months
RD cont	535	411	330	276	105	2
RD 18	541	414	337	276	55	2
MPT	547	391	312	249	60	1

Yearly Survival Probability:

Group	1 Year	2 Year	3 Year	4 Year	5 Year
RD cont	0.70	0.51	0.42	0.32	0.32
RD 18	0.74	0.41	0.22	0.14	0.14
MPT	0.72	0.45	0.24	0.16	0.08

Network meta-analysis (NMA)

A10. Please clarify if any pairwise meta-analysis was conducted for head-to-head comparisons of MPT vs MP. If so, please state whether the results were consistent with those of this comparison in the NMA, and whether there was statistical heterogeneity.

A separate pairwise meta-analysis for the MPT-melphalan prednisone (MP) contrast (Table 5 and Table 7) was not performed for the original company submission.

Given the structure of the network, the MPT-MP contrast is based only on direct head-to-head evidence as no other studies provide indirect estimates for this treatment contrast. As such, pairwise meta-analysis will yield the same hazard ratio for MPT vs. MP as those generated by network meta-analysis (NMA).

In the original submission, the Bayesian fixed-effects NMA generated the following hazard ratios for MPT vs. MP;

- Overall Survival (OS) = 0.63 [0.50, 0.78]
- PFS = 0.56 [0.46, 0.68]

In response to this clarification question, we performed a frequentist inverse variance weighted fixed-effects meta-analysis for the MPT-MP contrast. The associated results are identical for PFS (Table 8) to the results generated by the Bayesian NMA. The 0.01 difference in the hazard ratio for OS (Table 6) is due to the difference in methodology; Markov Chain Monte Carlo Simulation was used for the Bayesian NMA compared to the meta-analysis which used a frequentist inverse variance weighted approach.

Table 5: Constant hazard ratios for OS as reported in individual studies

Study	Reference	Intervention	HR	logHR(SE)
IFM-99/06	MP	MPT	0.59	-0.53 (0.144)
IFM 01/01	MP	MPT	0.68	-0.39 (0.175)

Key: MPT, melphalan, prednisone and thalidomide; **MP**, melphalan and prednisone; **HR**, hazard ratio; **SE**, standard error

Table 6: Meta-analysis of MPT vs. MP trials for OS

	log(HR)	se of log(HR)	variance	Weight (precision)	HR	95% CI (low)	95% CI (high)
IFM-99/06	-0.53	0.144	0.020736	48.22530864	0.59	0.44	0.78
IFM 01/01	-0.39	0.175	0.030625	32.65306122	0.68	0.48	0.95
Results							
FE pooled	-0.4735	0.1112			**0.62**	**0.50**	**0.77**
Inverse					**1.61**	**1.29**	**2.00**

Key: MPT, melphalan, prednisone and thalidomide; **MP**, melphalan and prednisone; **HR**, hazard ratio; **SE**, standard error; **FE**, fixed-effect

Table 7: Constant hazard ratios for PFS as reported in individual studies

Study	Reference	Intervention	HR	logHR(SE)
IFM-99/06	MP	MPT	0.51	-0.67 (0.134)
IFM 01/01	MP	MPT	0.62	-0.48 (0.145)

Key: MPT, melphalan, prednisone and thalidomide; **MP**, melphalan and prednisone; **HR**, hazard ratio; **SE**, standard error

Table 8: Meta-analysis of MPT vs. MP trials for PFS

	log(HR)	se of log(HR)	variance	Weight (precision)	HR	95% CI (low)	95% CI (high)
IFM-99/06	-0.67	0.134	0.017956	55.6916908	0.51	0.39	0.67
IFM 01/01	-0.48	0.145	0.021025	47.56242568	0.62	0.47	0.82
Results							
FE pooled	FE pooled	-0.5825	0.0984		**0.56**	**0.46**	**0.68**
Inverse					**1.79**	**1.48**	**2.17**

Key: MPT, melphalan, prednisone and thalidomide; **MP**, melphalan and prednisone; **HR**, hazard ratio; **SE**, standard error; **FE**, fixed-effect

A11. Please clarify what the dashed lines are in Figures 15 and 16 (page 68 and 70, Document B) – are these credible intervals around the respective hazard ratios (straight lines)?

The dashed lines represent the 95% credible intervals around the expected value for the hazard ratios, which are represented by the unbroken lines.

A12. On page 68 of Document B, with reference to the time-varying HRs for overall survival (OS), it is stated that the HR of Rd relative to MPT becomes "statistically significant at approximately 20 months". Likewise, on page 70 with reference to the time-varying HRs for PFS it is stated that the HR of Rd relative to MPT decreases over time with the difference becoming "statistically important at approximately 18 months". Please clarify what is meant by this, and how this was measured/quantified.

Figures 15 and 16 (on pages 68 and 70 of Document B respectively) represent the hazard ratios of interventions in the network versus MPT over the course of time as determined by the best fitting second-order fractional polynomial models for OS and PFS, respectively. The solid lines represent the point estimate of the hazard ratio and the dashed lines represent the 95% credible intervals.

For both OS and PFS, point estimates for the hazard ratio of Rd vs. MPT decrease over time. At the earlier time points (up to 20 months for OS and 18 months for PFS) the 95% credible intervals include 1 indicating that the difference between the two treatments is not statistically significant. From 20 months (OS) and 18 months (PFS) onward, the 95% credible interval excludes 1 implying a statistically significant difference favouring Rd.

A13. Please supply interpretation of the data in Tables 19 and 21 (page 69-71, Document B). For example, what does the size of the correlation values signify in terms of the goodness of the model fit?

The correlation values do not provide information about goodness of model fit; the model fit was determined solely by the Deviance Information Criterion (DIC). The fixed-effects fractional polynomial NMA models are presented in equations (1) and (2) below. Additional explanation of parameters d0 and d1 are provided in Table 9.

The first-order fractional polynomial fixed-effects NMA model can be expressed as follows:

$$\ln\left(h_{jkt}\right) = \beta_{0jk} + \beta_{1jk} t^{p} \qquad \text{with } t^{0} = \log(t), \quad p \in \{0,1\}$$

$$\begin{pmatrix} \beta_{0jk} \\ \beta_{1jk} \end{pmatrix} = \begin{cases} \begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \end{pmatrix} & \text{if } k = b, b \in \{A, B, C\} \\ \begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \end{pmatrix} + \begin{pmatrix} d_{0Ak} - d_{0Ab} \\ d_{1Ak} - d_{1Ab} \end{pmatrix} & \text{if } k \succ b \end{cases} \qquad (1)$$

where h_{jkt} reflects the underlying hazard rate in trial *j* for intervention *k* at time point *t* and is now described as a function of time *t* with treatment and study specific scale and shape

parameters β_{0jk} and β_{1jk}. If β_{1jk} equals 0, a constant log hazard function is obtained, reflecting exponentially distributed survival times. If $\beta_{1jk} \neq 0$ and p=1, a linear hazard function is obtained which corresponds to a Gompertz survival function. If $\beta_{1jk} \neq 0$ and p=0, a Weibull hazard function is obtained. The vectors $\begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \end{pmatrix}$ are trial-specific and reflect the true underlying scale and shape parameters of the comparator treatment *b*. The pooled difference in the scale parameter β_0 of the log hazard curve for treatment *k* relative to comparator treatment *b* is expressed as $d_{0Ak} - d_{0Ab}$ with $d_{0AA} = 0$. d_{0Ak} reflects the log hazard ratio at time point zero. The pooled difference in the shape parameter β_1 of the log hazard curve for treatment *k* relative to comparator treatment *b* is expressed as $d_{1Ak} - d_{1Ab}$. d_{1Ak} reflects the change in the log hazard ratio over time. For a proportional hazards model, d_{1Ak} equals 0. By incorporating d_{1Ak} in addition to d_{0Ak}, a multi-dimensional treatment effect is used.

The second order fractional polynomial fixed-effects NMA model used in this project can be expressed as follows:

$$\ln\left(h_{jkt}\right) = \begin{cases} \beta_{0jk} + \beta_{1jk} t^{p_1} + \beta_{2jk} t^{p_2} & p_1 \neq p_2 \\ \beta_{0jk} + \beta_{1jk} t^{p_1} + \beta_{2jk} t^{p_1} (\log t) & p_1 = p_2 \end{cases} \quad \text{with } t^0 = \log(t)$$

$$\begin{pmatrix} \beta_{0jk} \\ \beta_{1jk} \\ \beta_{2jk} \end{pmatrix} = \begin{cases} \begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \\ \mu_{2jb} \end{pmatrix} & if\ k = b, b \in \{A, B, C\} \\ \begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \\ \mu_{2jb} \end{pmatrix} + \begin{pmatrix} d_{0Ak} - d_{0Ab} \\ d_{1Ak} - d_{1Ab} \\ 0 \end{pmatrix} & if\ k \succ b \end{cases} \quad (2)$$

Here the additional shape parameter β_2 of the log hazard curve is assumed to be the same for all treatment groups within a study thereby assuming that treatment only has an effect on β_{0jk} and β_{1jk}. However, this additional parameter leads to better fit to the available data and therefore better estimates of the hazard ratios over time, despite not contributing directly to the hazard ratios.

Table 9: Explanation of parameters d_0 and d_1 from time-varying NMA

Parameter	Definition	Interpretation	Example
d0	The relative treatment effect on the scale parameter of the	The log(HR) at time point 0.	For OS under the best-fitting 2nd order FP model, the log(HR) of

	parametric log(HR) function (each treatment vs. MPT)		Rd vs MPT at time zero is -0.08963, meaning that patients in the Rd arm have a lower hazard for OS at time zero than patients in the MPT arm.
d1	The relative treatment effect on the first shape parameter of the parametric log(HR) function (each treatment vs. MPT)	The change in log(HR) over time. A positive value indicates an increasing log(HR)over time and a negative value indicates a decreasing log(HR) over time. A value significantly different from zero means statistically significant changes in the log(HR) over time.	For OS under the best-fitting 2nd order FP model, the d1 parameter is -0.00592 for the Rd vs. MPT comparison, meaning that the hazard ratio decreases over time.
correlation	Correlation between parameters d0 and d1	–	–

Key: Rd, lenalidomide and low-dose dexamethasone until disease progression; **MPT**, melphalan, prednisone and thalidomide; **HR**, hazard ratio; **SE**, standard error; **FP**, fractional polynomial; **OS**, overall survival

A14. **Priority question:** Please elaborate on the choice of fractional polynomial model for OS and PFS as shown in Table 10 and Table 11 in Appendix D (page 37 to 38). It appears that the model with the lowest Deviance Information Criterion (DIC) value was chosen, but were any other considerations taken into account in the choice of model fit? (E.g. the clinical plausibility of the model chosen with respect to PFS and OS curves as observed in the trials).

The DIC was the sole criterion used to select the statistical model to perform the NMA to estimate relative treatment effects regarding PFS and OS between the interventions compared based on the available data in each trial.[3] Since the aim of the NMA was primarily estimation rather than extrapolation of relative treatment effects we considered statistical criteria sufficient to identify an appropriate model for the NMA.

In the cost-effectiveness scenario analyses presented in the original company submission, the estimated hazard ratio at the maximum follow-up for the study/studies informing each comparison was carried forward and assumed to remain constant to avoid clinically implausible extrapolations of the hazard ratio.

A15. **Priority question**. Please supply the NMA results for OS and PFS for each of the other 5 fractional polynomial parametric survival models in Table 10 and Table 11 (Appendix D). Please provide these results in the same format as used in the main company submission document (e.g. Figures 15 and 16 and Tables 19 and 21). This will enable us to compare variation in HRs between different order models. In addition, please supply zero-order fractional polynomial results for OS and PFS. As we understand it, this corresponds to a proportional hazards estimation and will enable us to assess comparability with the constant HR NMA. Please provide updated base-case cost-effectiveness results based on each of these analyses.

Fractional polynomial NMA

The results obtained with the 6 fractional polynomial models (i.e. the best-fitting fractional polynomial model as presented in the original company submission and the other 5 models), all with a multivariate treatment effect on scale and the 1st shape parameter of the log-hazard function, are presented for each endpoint as follows;

- OS:
    - Table 10: model fit statistics
    - Table 11: estimated hazard ratios for all interventions vs. MPT at 6-monthly intervals from 0 to 90 months for each of the 6 fractional polynomial models
    - Table 12 – Table 17: basic parameter estimates for each of the 6 fractional polynomial models. The corresponding plots of the hazard ratios over time are presented in Figure 2 – Figure 7.
- PFS (EMA-censored MM-020 data):
    - Table 18: model fit statistics
    - Table 19: estimated hazard ratios for all interventions vs. MPT at 6-monthly intervals from 0 to 90 months for each of the 6 fractional polynomial models
    - Table 20 – Table 25: basic parameter estimates for each of the 6 fractional polynomial models. The corresponding plots of the hazard ratios over time are presented in Table 9 – Table 14.

Overall survival

Table 10: Model fit statistics for alternative fixed-effects NMA models with a multivariate treatment effect on scale and 1st shape parameter; OS

Model	Dbar	pD	DIC
Weibull (1st order FP with p=0); treatment effects on 1 scale (d0) and 1 shape parameter (d1)	2161.04	15.96	2177
Gompertz (1st order FP with p=1); treatment effects on 1 scale (d0) and 1 shape parameter (d1)	2129.07	15.93	2145
2nd order FP with p1=0, p2=0; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	2126.21	19.79	2146
2nd order FP with p1=0, p2=1; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	2124.13	19.87	2144
2nd order FP with p1=1, p2=0, treatment effects on 1 scale (d0) and 1 shape parameter (d1)*	**2118.10**	**19.90**	**2138**
2nd order FP with p1=1, p2=1, treatment effects on 1 scale (d0) and 1 shape parameter (d1)	2120.04	19.96	2140

*considered best fitting model. **Key: FP**, fractional polynomial**; DIC**, Deviance Information Criterion

Table 11: Estimated hazard ratios of competing interventions vs MPT obtained with alternative fixed-effects NMA with a multivariate treatment effect on scale and 1st shape parameter; OS

Intervention	Reference	Time point (months)	HR (95% CI) [1st order FP with p=0; Weibull]	HR (95% CI) [1st order FP with p=1; Gompertz]	HR (95% CI) [2nd order FP with p1=0 and p2=0]	HR (95% CI) [2nd order FP with p1=0 and p2=1]	HR (95% CI) [2nd order FP with p1=1 and p2=0]	HR (95% CI) [2nd order FP with p1=1 and p2=1]
RD18	MPT	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	66	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	78	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Intervention	Reference	Time point (months)	HR (95% CI) [1st order FP with p=0; Weibull]	HR (95% CI) [1st order FP with p=1; Gompertz]	HR (95% CI) [2nd order FP with p1=0 and p2=0]	HR (95% CI) [2nd order FP with p1=0 and p2=1]	HR (95% CI) [2nd order FP with p1=1 and p2=0]	HR (95% CI) [2nd order FP with p1=1 and p2=1]
MP	MPT	48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	66	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	78	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	66	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	78	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Intervention	Reference	Time point (months)	HR (95% CI) [1st order FP with p=0; Weibull]	HR (95% CI) [1st order FP with p=1; Gompertz]	HR (95% CI) [2nd order FP with p1=0 and p2=0]	HR (95% CI) [2nd order FP with p1=0 and p2=1]	HR (95% CI) [2nd order FP with p1=1 and p2=0]	HR (95% CI) [2nd order FP with p1=1 and p2=1]
RD	MPT	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	66	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	78	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: Rd, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **HR**, hazard ratio; **FP**, fractional polynomial

Weibull

Figure 2: Results of fixed-effects NMA of OS; treatment effects as hazard ratio over time relative to MPT as obtained with Weibull model; treatment effects on scale and shape parameter of the log-hazard function

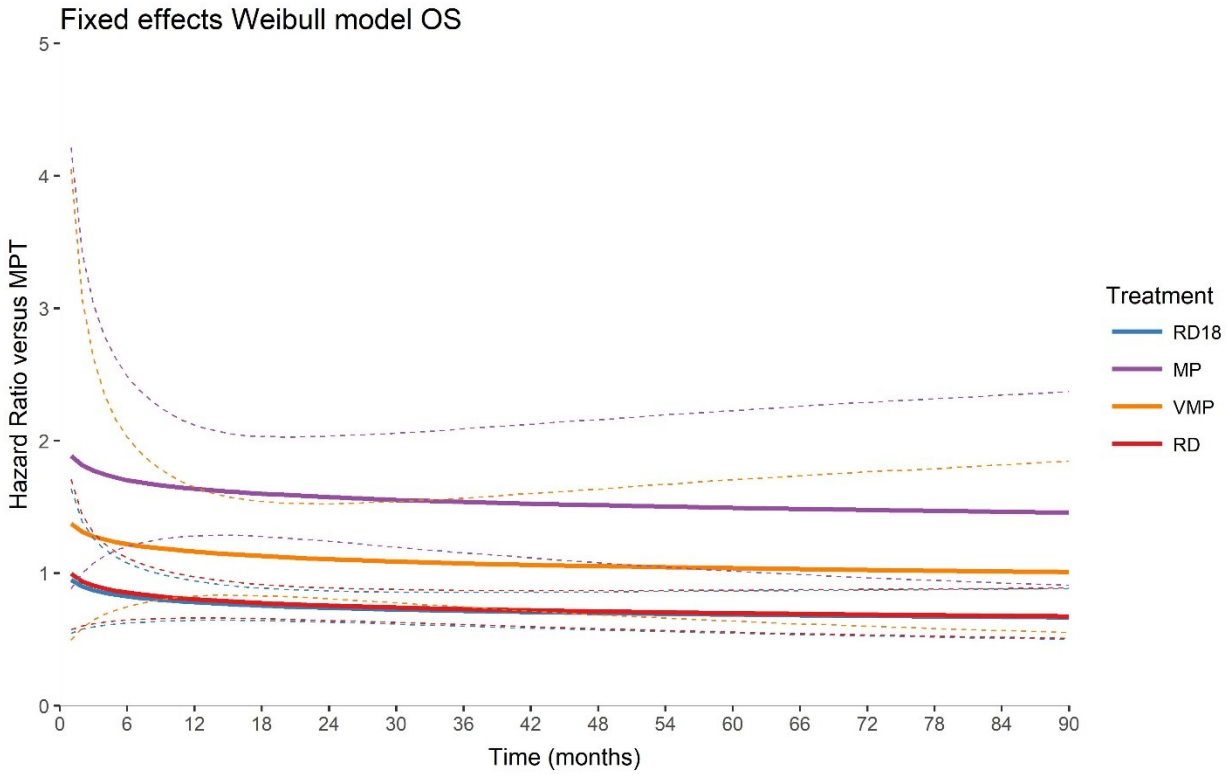


Table 12: Basic parameter estimates of Weibull model; OS; treatment effects on scale and shape parameter of the log-hazard function

	d0 estimate	d0 variance	d0 credible interval[1]	d1 estimate	d1 variance	d1 credible interval[1]	correlation
MPT		Reference		Reference			
Rd18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **FP**, fractional polynomial

Gompertz

Figure 3: Results of fixed-effects NMA of OS; treatment effects as hazard ratio over time relative to MPT as obtained with Gompertz model; treatment effects on scale and shape parameter of the log-hazard function

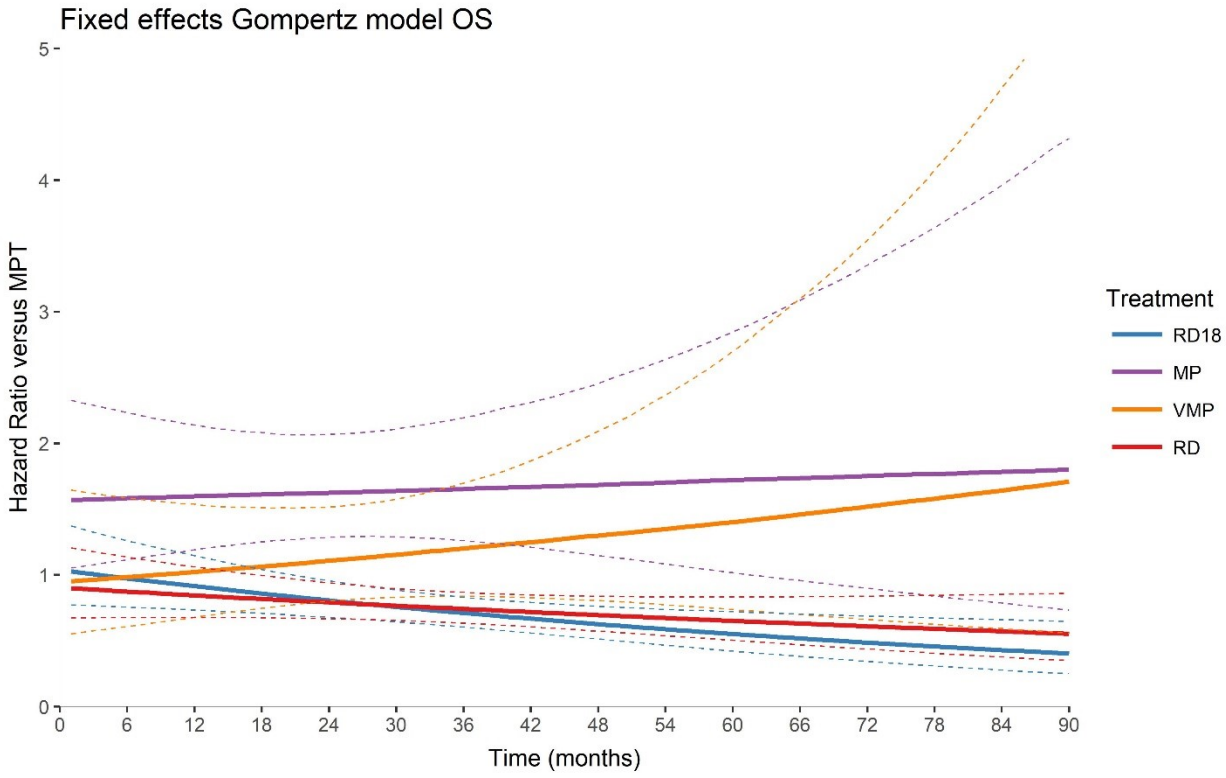


Table 13: Basic parameter estimates of Gompertz model; OS; treatment effects on scale and shape parameter of the log-hazard function

	d0 estimate	d0 variance	d0 credible interval[1]	d1 estimate	d1 variance	d1 credible interval[1]	correlation
MPT		Reference		Reference			
Rd18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone

2nd order fractional polynomial (p1=0, p2=0)

Figure 4: Results of fixed-effects NMA of OS; treatment effects as hazard ratio over time relative to MPT as obtained with 2nd order fractional polynomial model (P1 = 0, P2 = 0); treatment effects on scale and first shape parameter of the log-hazard function

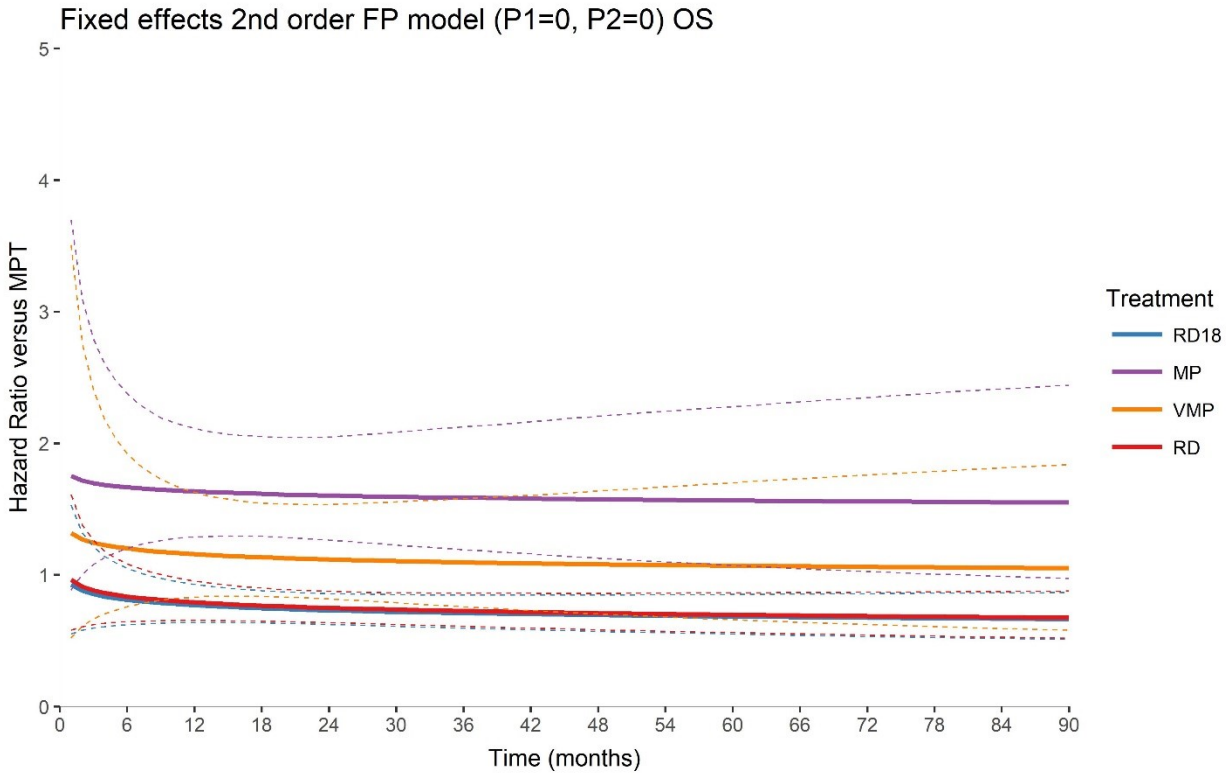


Table 14: Basic parameter estimates of 2nd order FP model (p_1=0, p_2=0); OS; treatment effects on scale and first shape parameter of the log-hazard function

	d0 estimate	d0 variance	d0 credible interval[1]	d1 estimate	d1 variance	d1 credible interval[1]	correlation
MPT		Reference		Reference			
Rd18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **FP**, fractional polynomial

2nd order fractional polynomial (p1=0, p2=1)

Figure 5: Results of fixed-effects NMA of OS; treatment effects as hazard ratio over time relative to MPT as obtained with 2nd order fractional polynomial model (P1 = 0, P2 = 1); treatment effects on scale and first shape parameter of the log-hazard function

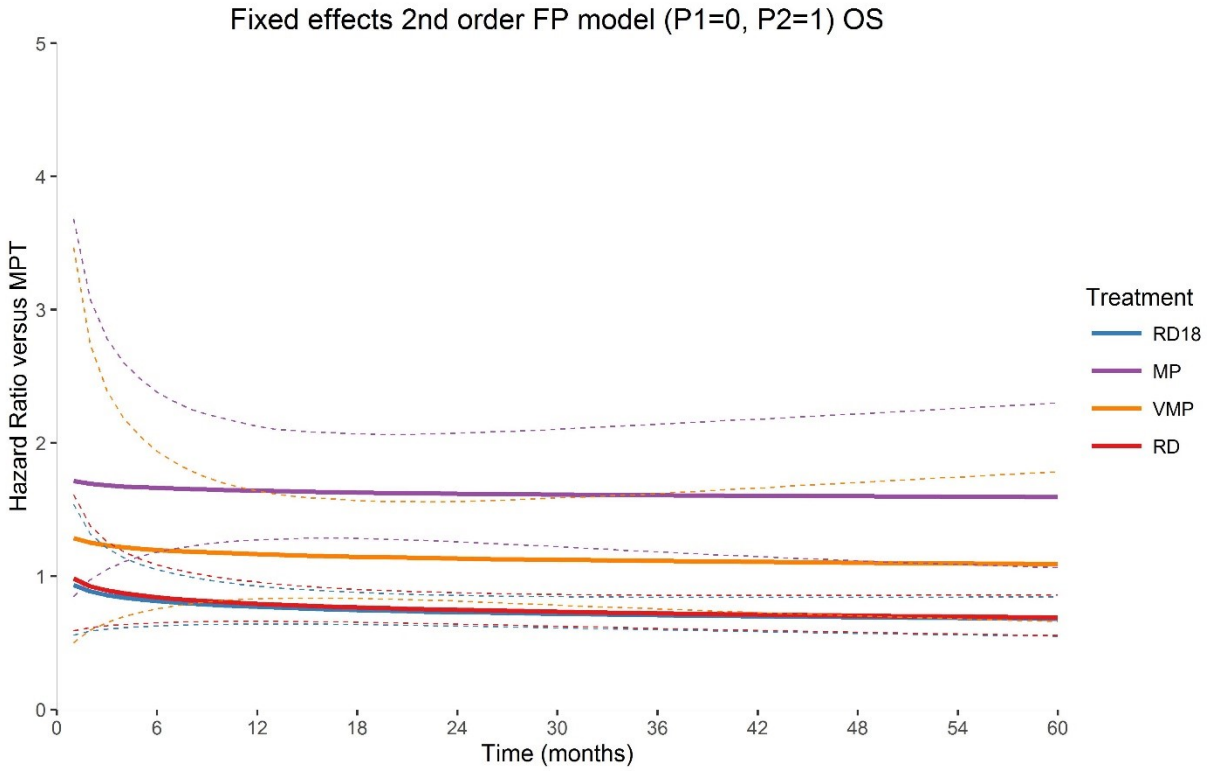


Table 15: Basic parameter estimates of 2nd order FP model (p_1=0, p_2=1); OS; treatment effects on scale and first shape parameter of the log-hazard function

	d0 estimate	d0 variance	d0 credible interval[1]	d1 estimate	d1 variance	d1 credible interval[1]	correlation
MPT		Reference		Reference			
Rd18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **FP**, fractional polynomial

2nd order fractional polynomial (p1=1, p2=0)

Figure 6: Results of fixed-effects NMA of OS; treatment effects as hazard ratio over time relative to MPT as obtained with 2nd order fractional polynomial model (P1 = 1, P2 = 0); treatment effects on scale and first shape parameter of the log-hazard function

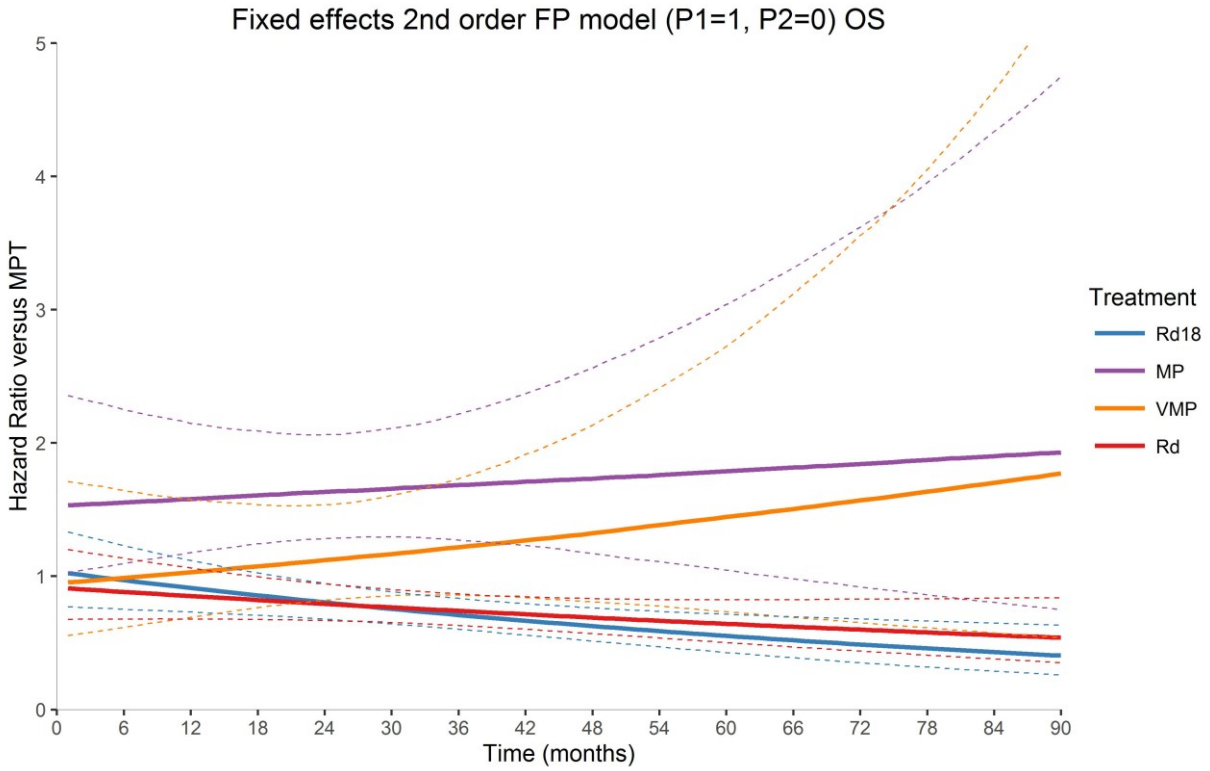


Table 16: Basic parameter estimates of 2nd order FP model (p_1=1, p_2=0); OS; treatment effects on scale and first shape parameter of the log-hazard function

	d0 estimate	d0 variance	d0 credible interval[1]	d1 estimate	d1 variance	d1 credible interval[1]	correlation
MPT		Reference		Reference			
Rd18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **FP**, fractional polynomial

2nd order fractional polynomial (p1=1, p2=1)

Figure 7: Results of fixed-effects NMA of OS; treatment effects as hazard ratio over time relative to MPT as obtained with 2nd order fractional polynomial model (P1 = 1, P2 = 1); treatment effects on scale and first shape parameter of the log-hazard function

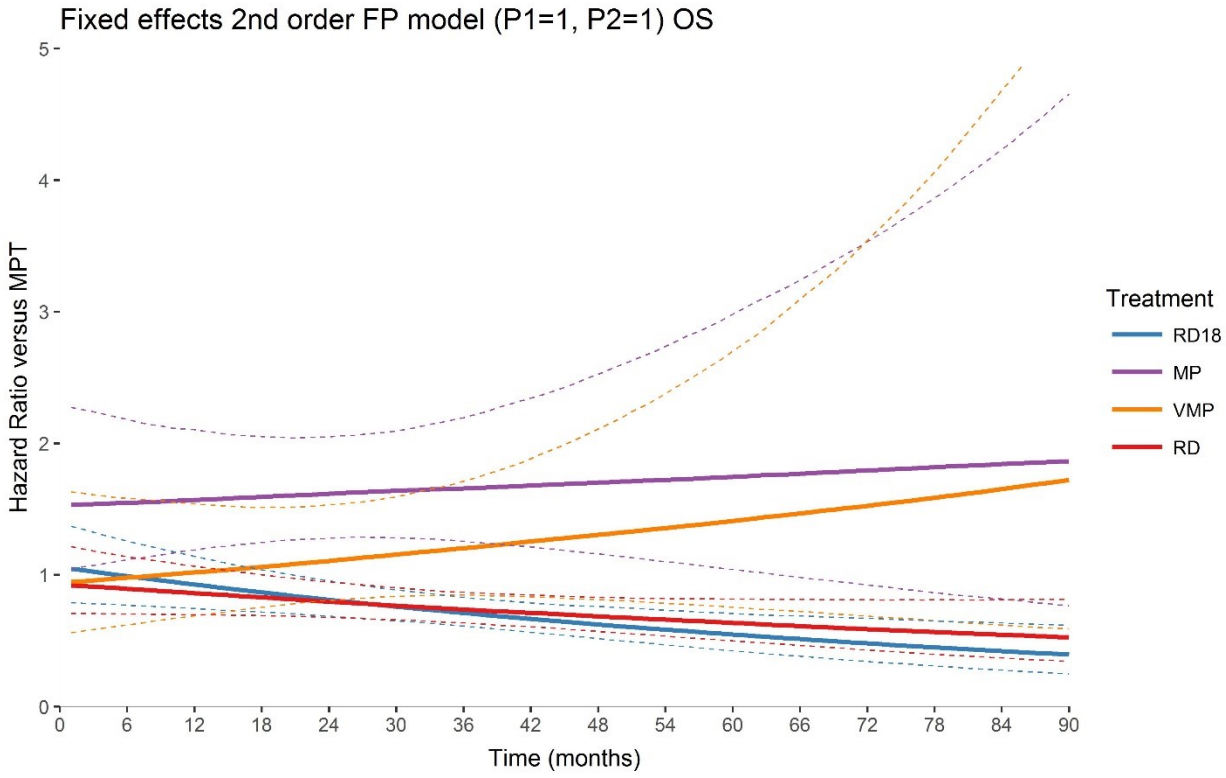


Table 17: Basic parameter estimates of 2nd order FP model (p_1=1, p_2=1); OS; treatment effects on scale and first shape parameter of the log-hazard function

	d0 estimate	d0 variance	d0 credible interval[1]	d1 estimate	d1 variance	d1 credible interval[1]	correlation
MPT		Reference		Reference			
Rd18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **FP**, fractional polynomial

Progression free survival, EMA-censored FIRST data

Table 18: Model fit statistics for alternative fixed-effects NMA models with a multivariate treatment effect on scale and 1st shape parameter; progression free survival, EMA-censored FIRST data

Model	Dbar	pD	DIC
Weibull (1st order FP with p=0); treatment effects on 1 scale (d0) and 1 shape parameter (d1)	1896.02	15.98	1912
Gompertz (1st order FP with p=1); treatment effects on 1 scale (d0) and 1 shape parameter (d1)	1900.22	15.78	1916
2nd order FP with p1=0, p2=0; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	1887.01	19.99	1907
2nd order FP with p1=0, p2=1; treatment effects on 1 scale (d0) and 1 shape parameter (d1)	1876.23	19.77	1896
2nd order FP with p1=1, p2=0, treatment effects on 1 scale (d0) and 1 shape parameter (d1)	1885.04	19.96	1905
2nd order FP with p1=1, p2=1, treatment effects on 1 scale (d0) and 1 shape parameter (d1)	**1875.04**	**19.96**	**1895**

Key: FP, fractional polynomial**; DIC**, Deviance Information Criterion

Table 19: Estimated hazard ratios of competing interventions vs MPT obtained with alternative fixed-effects NMA with a multivariate treatment effect on scale and 1st shape parameter; PFS, EMA-censored FIRST data

Intervention	Reference	Time point (months)	HR (95% CI) [1st order FP with p=0; Weibull]	HR (95% CI) [1st order FP with p=1; Gompertz]	HR (95% CI) [2nd order FP with p1=0 and p2=0]	HR (95% CI) [2nd order FP with p1=0 and p2=1]	HR (95% CI) [2nd order FP with p1=1 and p2=0]	HR (95% CI) [2nd order FP with p1=1 and p2=1]
RD18	MPT	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	66	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	78	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD18	MPT	90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Intervention	Reference	Time point (months)	HR (95% CI) [1st order FP with p=0; Weibull]	HR (95% CI) [1st order FP with p=1; Gompertz]	HR (95% CI) [2nd order FP with p1=0 and p2=0]	HR (95% CI) [2nd order FP with p1=0 and p2=1]	HR (95% CI) [2nd order FP with p1=1 and p2=0]	HR (95% CI) [2nd order FP with p1=1 and p2=1]
MP	MPT	48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	66	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	78	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	MPT	90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	66	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	78	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	MPT	90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Intervention	Reference	Time point (months)	HR (95% CI) [1st order FP with p=0; Weibull]	HR (95% CI) [1st order FP with p=1; Gompertz]	HR (95% CI) [2nd order FP with p1=0 and p2=0]	HR (95% CI) [2nd order FP with p1=0 and p2=1]	HR (95% CI) [2nd order FP with p1=1 and p2=0]	HR (95% CI) [2nd order FP with p1=1 and p2=1]
RD	MPT	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	66	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	78	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RD	MPT	90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: Rd, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **HR**, hazard ratio; **FP**, fractional polynomial

Weibull

Figure 8: Results of fixed-effects NMA of PFS; EMA-censored FIRST data; treatment effects as hazard ratio over time relative to MPT (as obtained with Weibull model); treatment effects on scale and shape parameter of the log-hazard function

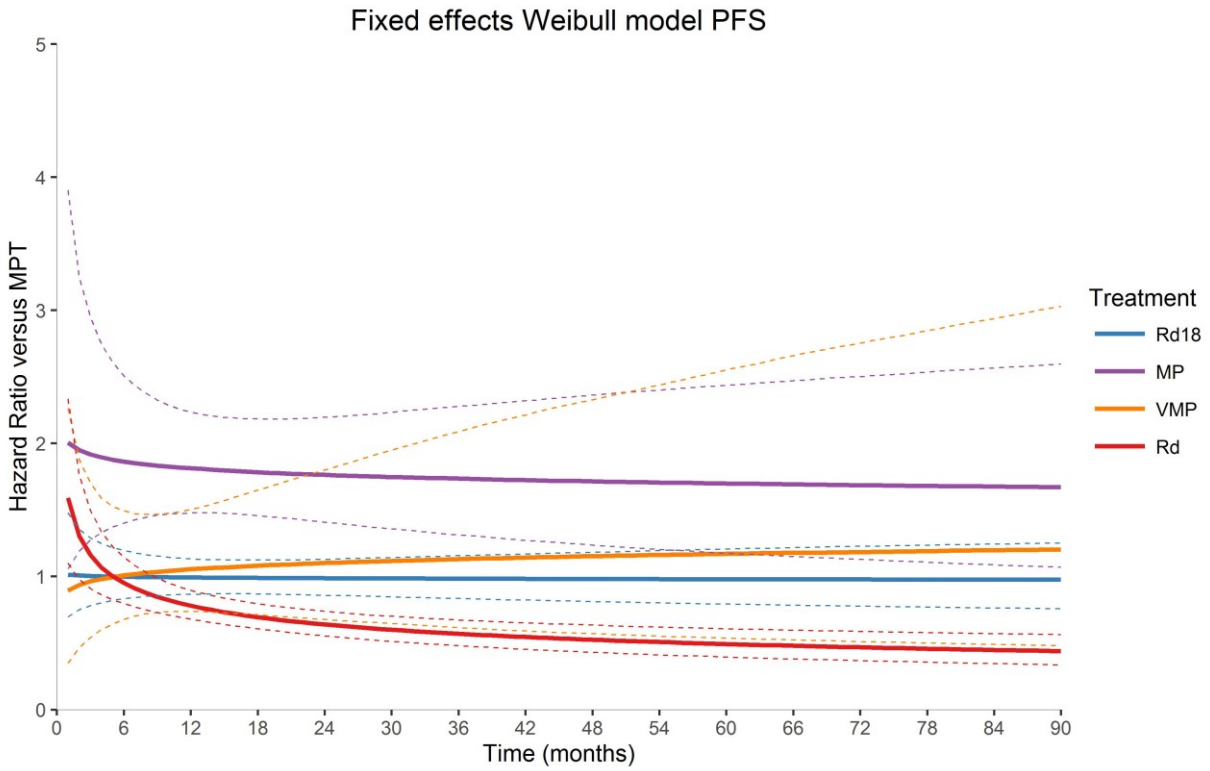


Table 20: Basic parameter estimates of Weibull model; PFS; EMA-censored FIRST data; treatment effects on scale and shape parameter of the log-hazard function

	d0 estimate	d0 variance	d0 credible interval[1]	d1 estimate	d1 variance	d1 credible interval[1]	correlation
MPT		Reference		Reference			
Rd18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone

Gompertz

Figure 9: Results of fixed-effects NMA of PFS; EMA-censored FIRST data; treatment effects as hazard ratio over time relative to MPT (as obtained with Gompertz model); treatment effects on scale and shape parameter of the log-hazard function

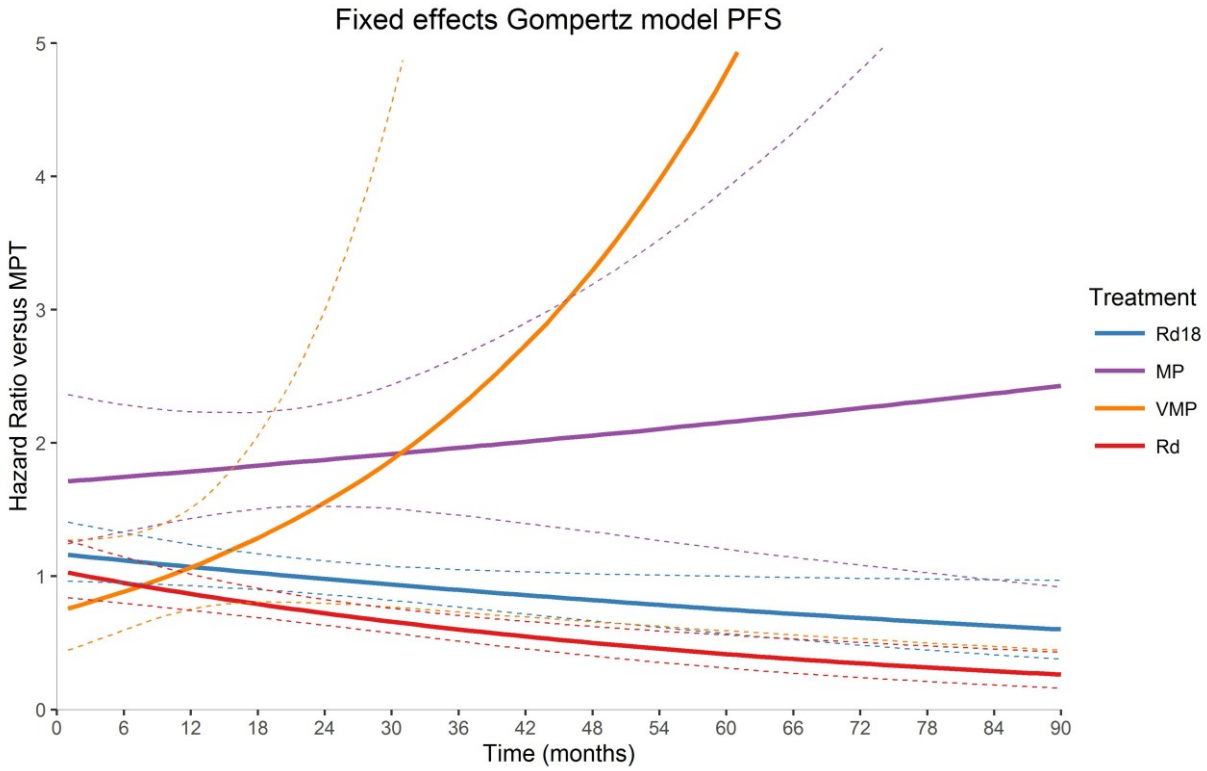


Table 21: Basic parameter estimates of Gompertz model; PFS; EMA-censored FIRST data; treatment effects on scale and shape parameter of the log-hazard function

	d0 estimate	d0 variance	d0 credible interval[1]	d1 estimate	d1 variance	d1 credible interval[1]	correlation
MPT		Reference		Reference			
Rd18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone

2nd order fractional polynomial (p1=0, p2=0)

Figure 10: Results of fixed-effects NMA of PFS; EMA-censored FIRST data; treatment effects as hazard ratio over time relative to MPT as obtained with 2nd order fractional polynomial model (p1 = 0, p2 = 0); treatment effects on scale and first shape parameter of the log-hazard function

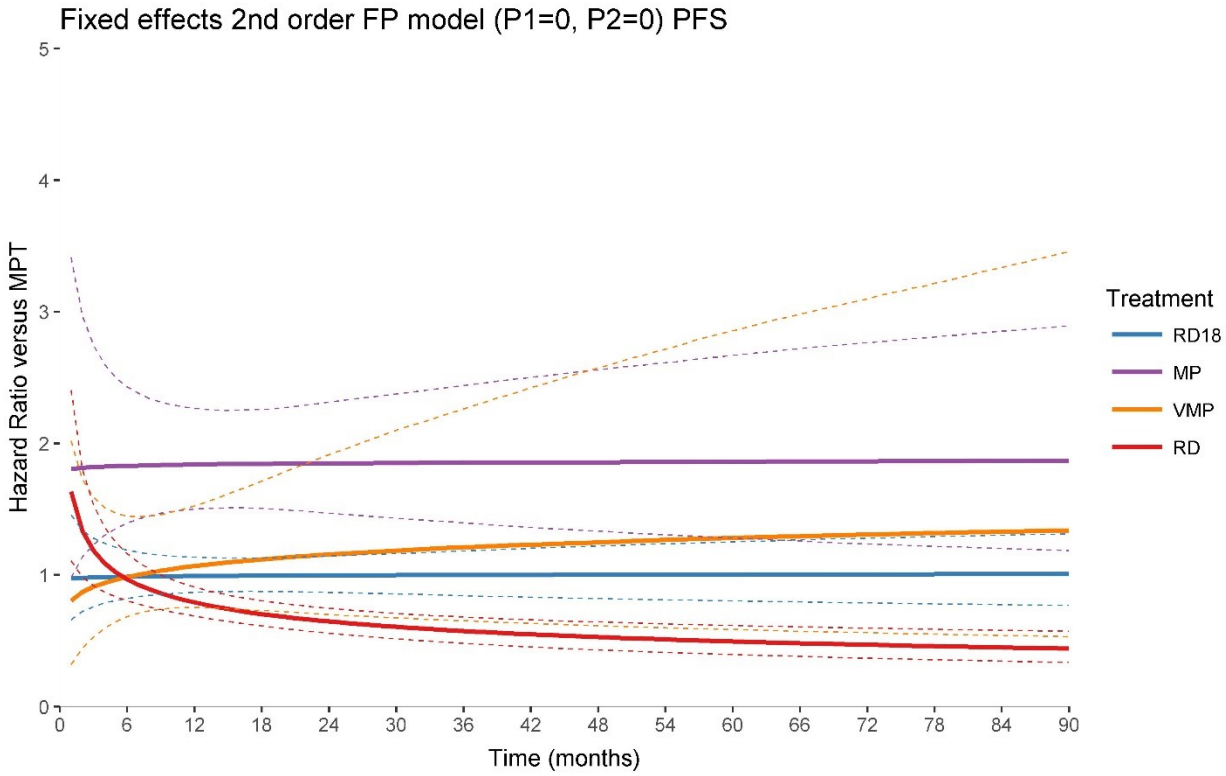


Table 22: Basic parameter of 2nd order FP model (p_1=0, p_2=0); PFS EMA-censored FIRST data; treatment effects on scale and first shape parameter of the log-hazard function

	d0 estimate	d0 variance	d0 credible interval[1]	d1 estimate	d1 variance	d1 credible interval[1]	correlation
MPT		Reference		Reference			
Rd18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **FP**, fractional polynomial

2nd order fractional polynomial (p1=0, p2=1)

Figure 11: Results of fixed-effects NMA of PFS; EMA-censored FIRST data; treatment effects as hazard ratio over time relative to MPT as obtained with 2nd order fractional polynomial model (p1 = 0, p2 = 1); treatment effects on scale and first shape parameter of the log-hazard function

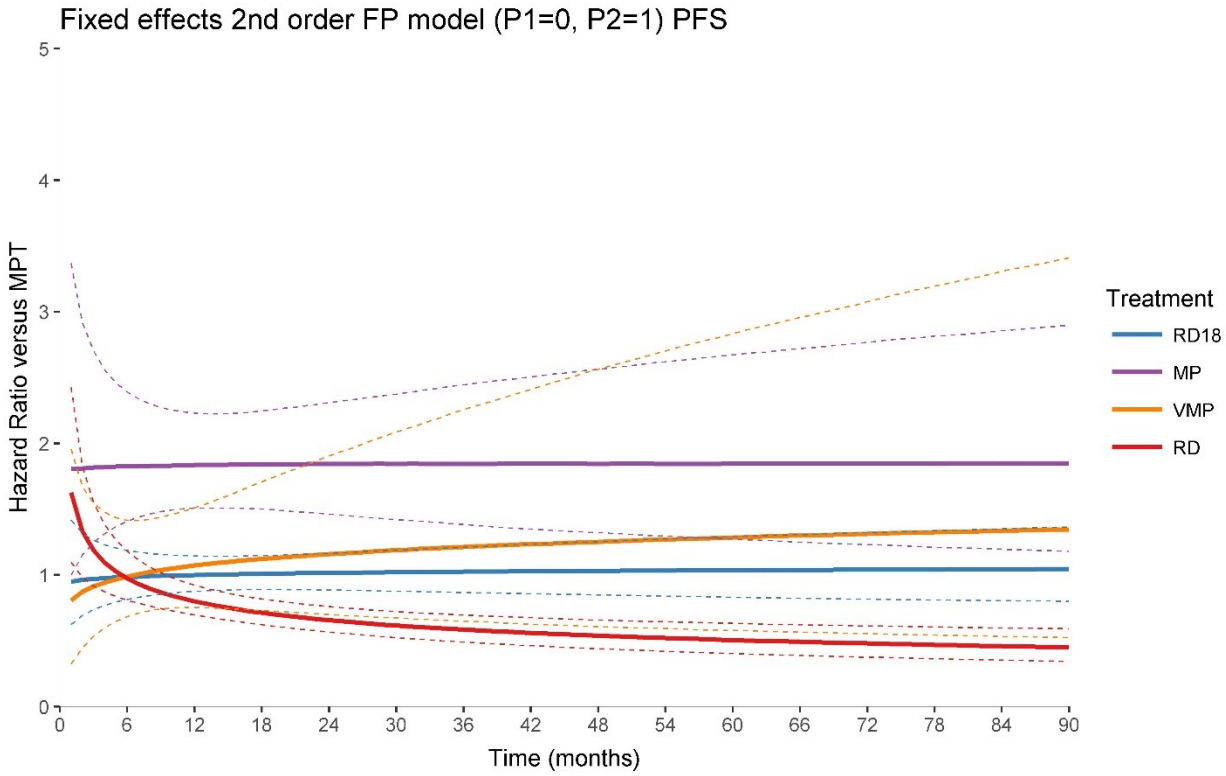


Table 23: Basic parameter of 2nd order FP model (p_1=0, p_2=1); PFS EMA-censored FIRST data; treatment effects on scale and first shape parameter of the log-hazard function

	d0 estimate	d0 variance	d0 credible interval[1]	d1 estimate	d1 variance	d1 credible interval[1]	correlation
MPT		Reference		Reference			
Rd18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] estimate ± 1.96*sqrt(variance) **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **FP**, fractional polynomial

2nd order fractional polynomial (p1=1, p2=0)

Figure 12: Results of fixed-effects NMA of PFS; EMA-censored FIRST data; treatment effects as hazard ratio over time relative to MPT as obtained with 2nd order fractional polynomial model (p1 = 1, p2 = 0); treatment effects on scale and first shape parameter of the log-hazard function

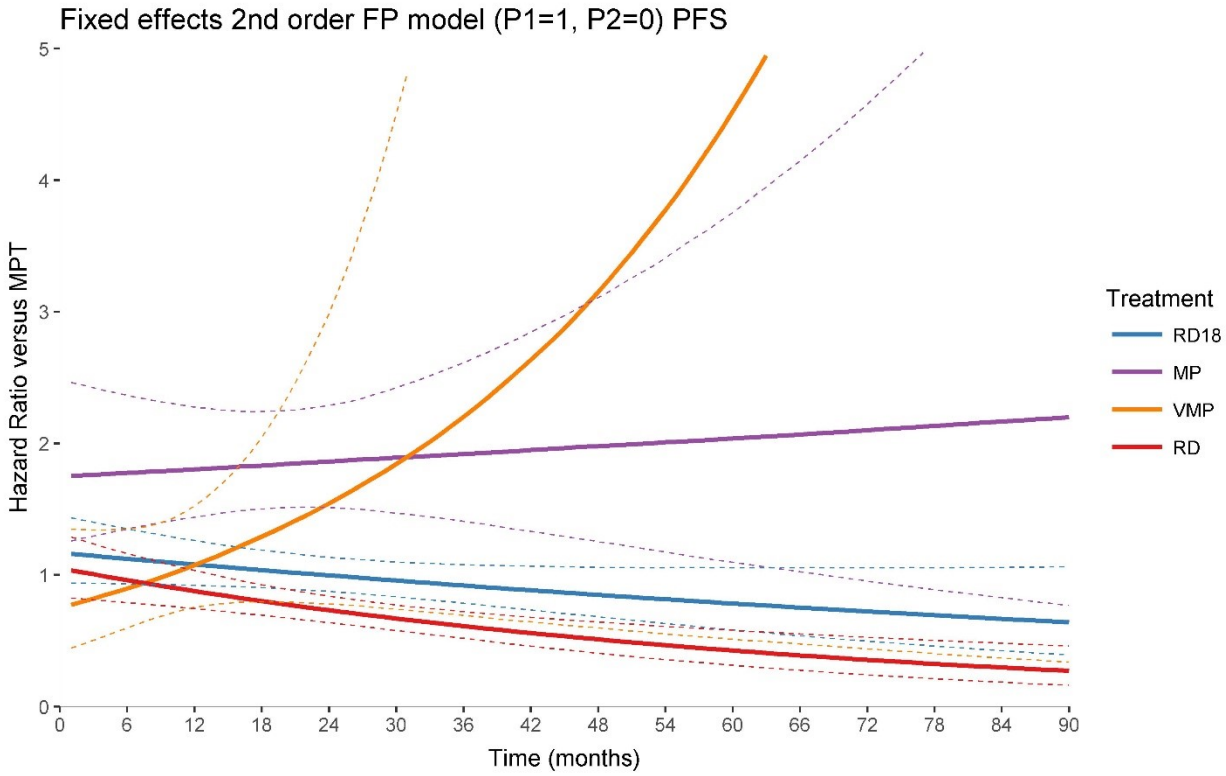


Table 24: Basic parameter of 2nd order FP model (p_1=1, p_2=0); PFS EMA-censored FIRST data; treatment effects on scale and first shape parameter of the log-hazard function

	d0 estimate	d0 variance	d0 credible interval[1]	d1 estimate	d1 variance	d1 credible interval[1]	correlation
MPT		Reference		Reference			
Rd18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] estimate ± 1.96*sqrt(variance) **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **FP**, fractional polynomial

2nd order fractional polynomial (p1=1, p2=1)

Figure 13: Results of fixed-effects NMA of PFS; EMA-censored FIRST data; treatment effects as hazard ratio over time relative to MPT as obtained with 2nd order fractional polynomial model (p1 = 1, p2 = 1); treatment effects on scale and first shape parameter of the log-hazard function

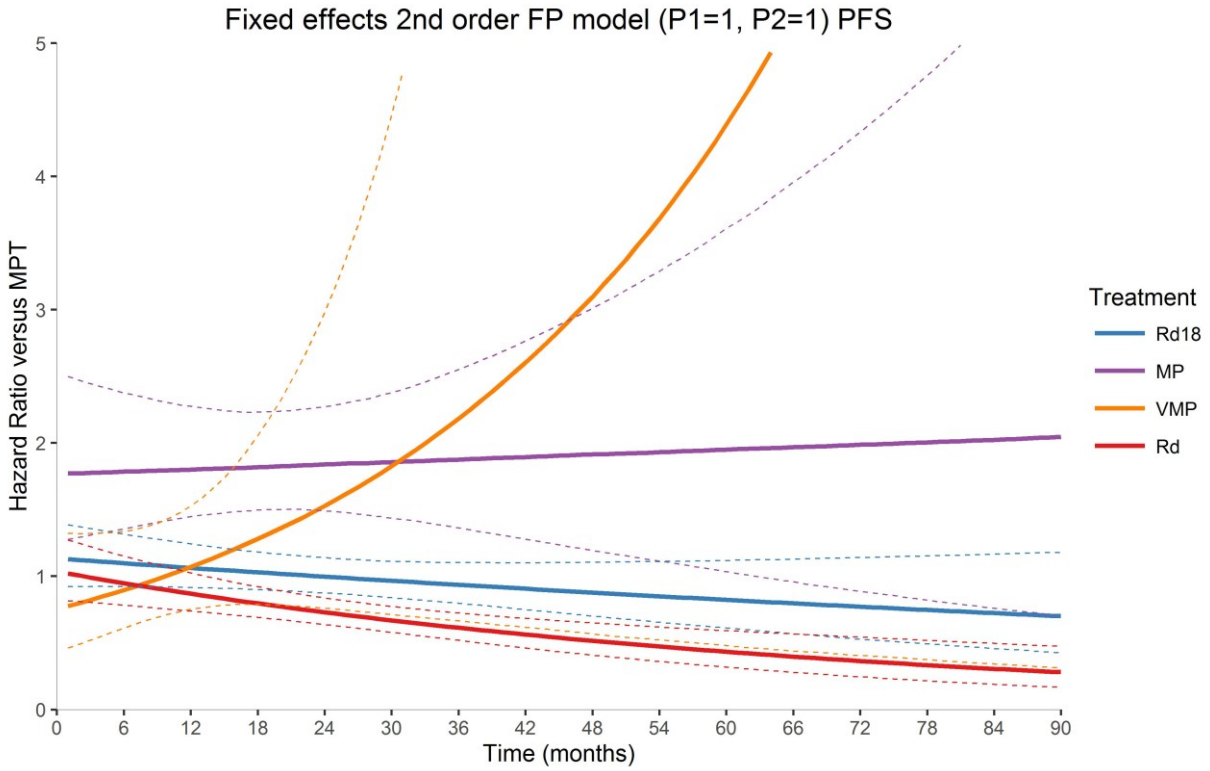


Table 25: Basic parameter of 2nd order FP model (p_1=1, p_2=1); PFS EMA-censored FIRST data; treatment effects on scale and first shape parameter of the log-hazard function

	d0 estimate	d0 variance	d0 credible interval[1]	d1 estimate	d1 variance	d1 credible interval[1]	correlation
MPT		Reference		Reference			
Rd18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VMP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **FP**, fractional polynomial

Fractional polynomial NMA with a treatment effect only on the scale parameter of the log-hazard function (i.e. assuming proportional hazards)

In response to the second part of this question, the NMA was run using each of the 6 fractional polynomial models with a treatment effect only on the scale parameter of the log-hazard function (i.e. assuming proportional hazards).

The question refers to these as “zero-order fractional polynomials”, however this is not a term the company would advocate using:

- The terms “first-order” and “second-order” relate to the number of time-related parameters of the parametric function describing the log hazard over time. The Gompertz or Weibull can be considered first-order models and have a scale and only 1 shape or time-related factor describing the change in hazard over time (i.e. time or log(time) respectively). Second-order models add an additional time-related factor and have therefore a scale and 2 shape parameters.

- A “zero-order” model would have no time-related parameter and hazard rates are therefore constant over time, i.e. an exponential survival distribution. With the fractional polynomials we can assume the treatment to affect only the scale parameters of the parametric hazard functions, the scale and the 1st shape parameter, or the scale and all shape parameters. In order to avoid over-fitting the second-order models we assumed the treatment to only have an impact on the scale and the first shape parameter.

In essence, the constant hazard ratio represents the average relative treatment effect over time, whereas the time-varying hazard ratio shows how the treatment effect changes over time. For both approaches it is important that the model has sufficient flexibility to capture the development of the hazards over time across all arms of the trials in the network in order to obtain unbiased estimates of either the constant or time-varying hazard ratios.

The fractional polynomial models with time-varying hazard ratios as well as the NMA based on study-specific reported constant hazard ratios (obtained with a Cox model with study specific non-parametric baseline hazards) allow to obtain valid time varying and constant hazard ratios with the NMA respectively.

Because the hazard ratios obtained from the best-fitting second-order fractional polynomial models with a treatment effect only on the scale parameter assume proportional hazards, the results are consistent with those obtained with the NMA based on reported hazard ratios (assuming a non-parametric baseline hazard).

For PFS, we are limited by the relatively short follow-up in the VISTA study (27 months). The fractional polynomial with constant hazard ratios puts too much constraint on the analyses resulting in constant hazard ratios for VMP vs. MPT (ranging between 0.87 and 0.91 depending on the model). These differ from the corresponding indirect comparison estimate based on study-specific hazard ratios (1.00; 95% CI 0.72, 1.38), although this difference is not statistically significant. This suboptimal fit to the data can also be observed by comparing

model fit statistics between the fractional polynomial with (Table 18) and without (Table 34) the assumption of time-varying hazard ratios for PFS; the former has a better fit.

Results for these analyses are presented as follows:

- OS
    - Table 10: model fit statistics
    - Table 11: estimated hazard ratios for all interventions vs. MPT for each of the 6 fractional polynomial models
    - Table 12 – Table 17: basic parameter estimates for each of the 6 fractional polynomial models.
- PFS (EMA-censored MM-020 data)
    - Table 26: model fit statistics
    - Table 27: estimated hazard ratios for all interventions vs. MPT for each of the 6 fractional polynomial models
    - Table 28 – Table 33: basic parameter estimates for each of the 6 fractional polynomial models.

Overall survival

Table 26: Model fit statistics for alternative fixed-effects NMA models with a treatment effect only on the scale parameter of the log-hazard function; OS

Model	Dbar	pD	DIC
Weibull (1st order FP with p=0); treatment effects on 1 scale (d0) parameter; proportional hazards	2158.01	11.99	2170
Gompertz (1st order FP with p=1); treatment effects on 1 scale (d0) parameter; proportional hazards	2133.92	12.08	2146
2nd order FP with p1=0, p2=0; treatment effects on 1 scale (d0) parameter; proportional hazards	2123.03	15.97	2139
2nd order FP with p1=0, p2=1; treatment effects on 1 scale (d0) parameter; proportional hazards	**2122.09**	**15.91**	**2138**
2nd order FP with p1=1, p2=0, treatment effects on 1 scale (d0) parameter; proportional hazards	**2121.95**	**16.05**	**2138**
2nd order FP with p1=1, p2=1, treatment effects on 1 scale (d0) parameter; proportional hazards	2124.06	15.94	2140

Key: FP, fractional polynomial**; DIC**, Deviance Information Criterion

Table 27: Estimated hazard ratios of competing interventions vs MPT obtained with alternative fixed-effects NMA with a treatment effect only on the scale parameter; OS

Intervention	Reference	HR (95% CI) [NMA based on study specific HRs]	HR (95% CI) [1st order FP with p=0; Weibull]	HR (95% CI) [1st order FP with p=1; Gompertz]	HR (95% CI) [2nd order FP with p1=0 and p2=0]	HR (95% CI) [2nd order FP with p1=0 and p2=1]	HR (95% CI) [2nd order FP with p1=1 and p2=0]	HR (95% CI) [2nd order FP with p1=1 and p2=1]
RD18	MPT	0.77 (0.66, 0.90)	0.74 (0.63, 0.86)	0.74 (0.63, 0.86)	0.74 (0.63, 0.86)	0.73 (0.63, 0.86)	0.74 (0.63, 0.86)	0.73 (0.63, 0.86)
MP	MPT	1.60 (1.28, 1.99)	1.59 (1.27, 2.02)	1.62 (1.28, 2.09)	1.61 (1.27, 2.07)	1.64 (1.31, 2.07)	1.62 (1.29, 2.06)	1.61 (1.29, 2.04)
VMP	MPT	1.11 (0.82, 1.50)	1.12 (0.83, 1.51)	1.14 (0.83, 1.57)	1.13 (0.82, 1.55)	1.15 (0.84, 1.56)	1.14 (0.85, 1.56)	1.14 (0.84, 1.54)
RD	MPT	0.78 (0.67, 0.91)	0.76 (0.65, 0.88)	0.75 (0.64, 0.89)	0.75 (0.65, 0.88)	0.75 (0.64, 0.88)	0.75 (0.64, 0.89)	0.75 (0.64, 0.88)

Key: Rd, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **HR**, hazard ratio; **FP**, fractional polynomial

Weibull

Table 28: Basic parameter estimates of Weibull model; OS; treatment effects only on scale parameter of the log-hazard function (i.e. proportional hazards assumption)

	d0 estimate (log(HR))	d0 variance	d0 credible interval[1]
MPT	Reference	Reference	Reference
Rd18	-0.30160	0.00654	(-0.46010, -0.14310)
MP	0.46560	0.01412	(0.23273, 0.69847)
VMP	0.11610	0.02410	(-0.18814, 0.42034)
Rd	-0.27700	0.00626	(-0.43203, -0.12197)

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **HR**, hazard ratio

Gompertz

Table 29: Basic parameter estimates of Gompertz model; OS; treatment effects only on scale parameter of the log-hazard function (i.e. proportional hazards assumption)

	d0 estimate (log(HR))	d0 variance	d0 credible interval[1]
MPT	Reference	Reference	Reference
Rd18	-0.30590	0.00670	(-0.46632, -0.14548)
MP	0.48280	0.01508	(0.24209,0.72351)
VMP	0.12640	0.02650	(-0.19268 ,0.44548)
Rd	-0.28360	0.00664	(-0.44335, -0.12385)

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **HR**, hazard ratio

2nd order fractional polynomial (p1=0, p2=0)

Table 30: Basic parameter estimates of 2nd order FP model (p_1=1, p_2=0); OS; treatment effects only on scale parameter of the log-hazard function (i.e. proportional hazards assumption)

	d0 estimate (log(HR))	d0 variance	d0 credible interval[1]
MPT	Reference	Reference	Reference
Rd18	-0.30780	0.00656	(-0.4666, -0.149)
MP	0.47900	0.01489	(0.23981, 0.71819)
VMP	0.12530	0.02572	(-0.18902, 0.43962)
Rd	-0.28290	0.00644	(-0.44021, -0.12559)

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **HR**, hazard ratio; **FP**, fractional polynomial

2nd order fractional polynomial (p1=0, p2=1)

Table 31: Basic parameter estimates of 2nd order FP model (p_1=0, p_2=1); OS; treatment effects only on scale parameter of the log-hazard function (i.e. proportional hazards assumption)

	d0 estimate (log(HR))	d0 variance	d0 credible interval[1]
MPT	Reference	Reference	Reference
Rd18	-0.308	0.00637	(-0.46441, -0.15159)
MP	0.4962	0.014	(0.26427, 0.72813)
VMP	0.1427	0.02508	(-0.16773, 0.45313)
Rd	-0.2839	0.00638	(-0.44046, -0.12734)

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **HR**, hazard ratio; **FP**, fractional polynomial

2nd order fractional polynomial (p1=1, p2=0)

Table 32: Basic parameter estimates of 2nd order FP model (p_1=1, p_2=0); OS; treatment effects only on scale parameter of the log-hazard function (i.e. proportional hazards assumption)

	d0 estimate (log(HR))	d0 variance	d0 credible interval[1]
MPT	Reference	Reference	Reference
Rd18	-0.30470	0.00676	(-0.46579, -0.14361)
MP	0.48415	0.01450	(0.24815, 0.72015)
VMP	0.13365	0.02430	(-0.17189, 0.43919)
Rd	-0.28160	0.00674	(-0.44254, -0.12066)

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **HR**, hazard ratio; **FP**, fractional polynomial

2nd order fractional polynomial (p1=1, p2=1)

Table 33: Basic parameter estimates of 2nd order FP model (p_1=1, p_2=1); OS; treatment effects only on scale parameter of the log-hazard function (i.e. proportional hazards assumption)

	d0 estimate (log(HR))	d0 variance	d0 credible interval[1]
MPT	Reference	Reference	Reference
Rd18	-0.31135	0.00678	(-0.4727, -0.15)
MP	0.47780	0.01382	(0.2474, 0.7082)
VMP	0.12790	0.02392	(-0.17523, 0.43103)
Rd	-0.28830	0.00664	(-0.44803, -0.12857)

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **HR**, hazard ratio; **FP**, fractional polynomial

Progression free survival, EMA-censored FIRST data

Table 34: Model fit statistics for alternative fixed-effects NMA models with a treatment effect only on the scale parameter of the log-hazard function; progression free survival; EMA-censored FIRST data

Model	Dbar	pD	DIC
Weibull (1st order FP with p=0); treatment effects on 1 scale (d0) parameter; proportional hazards	1916.99	12.01	1929
Gompertz (1st order FP with p=1); treatment effects on 1 scale (d0) parameter; proportional hazards	1920.98	12.02	1933
2nd order FP with p1=0, p2=0; treatment effects on 1 scale (d0) parameter; proportional hazards	1907.04	15.96	1923
2nd order FP with p1=0, p2=1; treatment effects on 1 scale (d0) parameter; proportional hazards	1897.03	15.97	1913
2nd order FP with p1=1, p2=0, treatment effects on 1 scale (d0) parameter; proportional hazards	1896.89	16.11	1913
2nd order FP with p1=1, p2=1, treatment effects on 1 scale (d0) parameter; proportional hazards	**1887.04**	**15.96**	**1903**

Key: FP, fractional polynomial**; DIC**, Deviance Information Criterion

Table 35: Estimated hazard ratios of competing interventions vs MPT obtained with alternative fixed-effects NMA with a treatment effect only on the scale parameter; progression free survival EMA-censored FIRST data

Intervention	Reference	HR (95% CI) [NMA based on study specific HRs]	HR (95% CI) [1st order FP with p=0; Weibull]	HR (95% CI) [1st order FP with p=1; Gompertz]	HR (95% CI) [2nd order FP with p1=0 and p2=0]	HR (95% CI) [2nd order FP with p1=0 and p2=1]	HR (95% CI) [2nd order FP with p1=1 and p2=0]	HR (95% CI) [2nd order FP with p1=1 and p2=1]
RD18	MPT	1.03 (0.90, 1.18)	0.99 (0.87, 1.13)	1.00 (0.88, 1.13)	1.00 (0.87, 1.13)	1.00 (0.88, 1.14)	1.00 (0.88, 1.14)	1.01 (0.89, 1.15)
MP	MPT	1.79 (1.47, 2.17)	1.79 (1.48, 2.19)	1.84 (1.51, 2.24)	1.83 (1.51, 2.24)	1.83 (1.49, 2.23)	1.83 (1.51, 2.25)	1.82 (1.50, 2.24)
VMP	MPT	1.00 (0.72, 1.38)	0.87 (0.62, 1.23)	0.91 (0.65, 1.28)	0.89 (0.63, 1.24)	0.89 (0.63, 1.26)	0.89 (0.63, 1.26)	0.88 (0.63, 1.24)
RD	MPT	0.74 (0.65, 0.85)	0.72 (0.63, 0.82)	0.73 (0.64, 0.83)	0.73 (0.63, 0.83)	0.73 (0.64, 0.84)	0.74 (0.64, 0.84)	0.74 (0.65, 0.84)

Key: Rd, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **HR**, hazard ratio; **FP**, fractional polynomial

Weibull

Table 36: Basic parameter estimates of Weibull model; PFS; EMA-censored FIRST data; treatment effects only on scale parameter of the log-hazard function (i.e. proportional hazards assumption)

	d0 estimate (log(HR))	d0 variance	d0 credible interval[1]
MPT	Reference	Reference	Reference
Rd18	-0.00856	0.00428	(-0.13684, 0.11972)
MP	0.58450	0.01020	(0.38659, 0.78241)
VMP	-0.13370	0.03037	(-0.47528, 0.20788)
Rd	-0.33480	0.00461	(-0.46781, -0.20179)

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **HR**, hazard ratio

Gompertz

Table 37: Basic parameter estimates of Gompertz model; PFS; EMA-censored FIRST data; treatment effects only on scale parameter of the log-hazard function (i.e. proportional hazards assumption)

	d0 estimate (log(HR))	d0 variance	d0 credible interval[1]
MPT	Reference	Reference	Reference
Rd18	-0.00414	0.00418	(-0.13081, 0.12252)
MP	0.60780	0.01015	(0.41035, 0.80525)
VMP	-0.09054	0.02985	(-0.42918, 0.2481)
Rd	-0.31680	0.00469	(-0.45099, -0.18261)

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **HR**, hazard ratio

2nd order fractional polynomial (p1=0, p2=0)

Table 38: Basic parameter of 2nd order FP model (p_1=0, p_2=0); PFS EMA-censored FIRST data; treatment effects only on scale parameter of the log-hazard function (i.e. proportional hazards assumption)

	d0 estimate (log(HR))	d0 variance	d0 credible interval[1]
MPT	Reference	Reference	Reference
Rd18	-0.00252	0.00438	(-0.13228, 0.12724)
MP	0.60610	0.01021	(0.40801, 0.80419)
VMP	-0.11520	0.03003	(-0.45488, 0.22448)
Rd	-0.31870	0.00487	(-0.45541, -0.18199)

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **HR**, hazard ratio; **FP**, fractional polynomial

2nd order fractional polynomial (p1=0, p2=1)

Table 39: Basic parameter of 2nd order FP model (p_1=0, p_2=1); PFS EMA-censored FIRST data; treatment effects only on scale parameter of the log-hazard function (i.e. proportional hazards assumption)

	d0 estimate (log(HR))	d0 variance	d0 credible interval[1]
MPT	Reference	Reference	Reference
Rd18	0.00353	0.00427	(-0.12454, 0.13159)
MP	0.60310	0.01044	(0.40283, 0.80337)
VMP	-0.11480	0.03154	(-0.4629, 0.2333)
Rd	-0.30970	0.00466	(-0.44351, -0.17589)

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **HR**, hazard ratio; **FP**, fractional polynomial

2nd order fractional polynomial (p1=0, p2=0)

Table 40: Basic parameter of 2nd order FP model (p_1=1, p_2=0); PFS EMA-censored FIRST data; treatment effects only on scale parameter of the log-hazard function (i.e. proportional hazards assumption)

	d0 estimate (log(HR))	d0 variance	d0 credible interval[1]
MPT	Reference	Reference	Reference
Rd18	0.00514	0.00435	(-0.12412, 0.1344)
MP	0.60445	0.01033	(0.40527, 0.80363)
VMP	-0.11585	0.03083	(-0.46, 0.2283)
Rd	-0.30650	0.00480	(-0.44224, -0.17076)

[1] estimate ± 1.96*sqrt(variance) . **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **HR**, hazard ratio; **FP**, fractional polynomial

2nd order fractional polynomial (p1=1, p2=1)

Table 41: Basic parameter of 2nd order FP model (p_1=1, p_2=1); PFS EMA-censored FIRST data; treatment effects only on scale parameter of the log-hazard function (i.e. proportional hazards assumption)

	d0 estimate (log(HR))	d0 variance	d0 credible interval[1]
MPT	Reference	Reference	Reference
Rd18	0.01266	0.00420	(-0.11436, 0.13968)
MP	0.59880	0.01024	(0.40045, 0.79715)
VMP	-0.12985	0.03023	(-0.47063, 0.21093)
Rd	-0.30495	0.00452	(-0.43678, -0.17312)

[1] estimate ± 1.96*sqrt(variance). **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone; **HR**, hazard ratio; **FP**, fractional polynomial

Cost-effectiveness results

Cost-effectiveness results for each of the fractional polynomial models provided above are detailed in Table 42. These scenarios were conducted as follows:

- The HRs from the fractional polynomial NMA models were used to predict PFS and OS for both Rd and bortezomib in combination with melphalan and prednisone (VMP)
- The estimated HR at the maximum follow-up for each treatment are applied for lifetime (as described in Section B.3.3.2 of the original company submission)
- When the NMA model is varied for PFS, the model used for OS remains the same as the original company base case (i.e. constant hazard ratio for VMP vs. MPT, and the MSM distribution for Rd), and vice versa when OS is varied. This is indicated in the second part of the "Model" column in Table 42.

Rd remains cost-effective vs. VMP using all models, with scenarios using the fractional polynomials all providing lower incremental cost-effectiveness ratios (ICERs) than the original company base case ([redacted] per quality adjusted life year (QALY)).

The "Time-varying HRs" worksheet has been adapted in the Excel model provided as part of the clarification responses to include all fractional polynomial models and switches (columns C:G and AH:BE changed), and in the "Scenario Analysis" worksheet, rows 16:39 have been amended to test ICERs for all FP models.

Table 42: Cost-effectiveness results with alternative fractional polynomial survival models

Model		DIC	ICER
Base case (constant hazard ratios)		NA	[redacted]
2nd order fractional polynomials			
PFS FP models: Weibull	OS, VMP constant HR versus MPT and Rd MSM distribution	1912	[redacted]
PFS FP models: Gompertz		1916	[redacted]
PFS FP models: 2nd order fractional polynomial model (P1 = 0, P2 = 0)		1907	[redacted]
PFS FP models: 2nd order fractional polynomial model (P1 = 0, P2 = 1)		1896	[redacted]
PFS FP models: 2nd order fractional polynomial model (P1 = 1, P2 = 0)		1905	[redacted]
PFS FP models: 2nd order fractional polynomial model (P1 = 1, P2 = 1)		**1895**	[redacted]
OS FP models: Weibull	PFS, VMP constant HR versus MPT and Rd MSM distribution	2177	[redacted]
OS FP models: Gompertz		2145	[redacted]
OS FP models: 2nd order fractional polynomial model (P1 = 0, P2 = 0)		2146	[redacted]
OS FP models: 2nd order fractional polynomial model (P1 = 0, P2 = 1)		2144	[redacted]
OS FP models: 2nd order fractional polynomial model (P1 = 1, P2 = 0)		**2138**	[redacted]
OS FP models: 2nd order fractional polynomial model (P1 = 1, P2 = 1)		2140	[redacted]
"0 order" proportional hazard fractional polynomials			
PFS FP models, proportional hazards: Weibull	OS, VMP constant HR versus MPT and Rd MSM distribution	1929	[redacted]
PFS FP models, proportional hazards: Gompertz		1933	[redacted]
PFS FP models, proportional hazards: 2nd order fractional polynomial model (P1 = 0, P2 = 0)		1923	[redacted]
PFS FP models, proportional hazards: 2nd order fractional polynomial model (P1 = 0, P2 = 1)		1913	[redacted]
PFS FP models, proportional hazards: 2nd order fractional polynomial model (P1 = 1, P2 = 0)		1913	[redacted]
PFS FP models, proportional hazards: 2nd order fractional polynomial model (P1 = 1, P2 = 1)		**1903**	[redacted]
OS FP models, proportional hazards: Weibull	PFS, VMP constant HR versus MPT and Rd MSM distribution	2170	[redacted]
OS FP models, proportional hazards: Gompertz		2146	[redacted]
OS FP models, proportional hazards: 2nd order fractional polynomial model (P1 = 0, P2 = 0)		2139	[redacted]
OS FP models, proportional hazards: 2nd order fractional polynomial model (P1 = 0, P2 = 1)		**2138**	[redacted]
OS FP models, proportional hazards: 2nd order fractional polynomial model (P1 = 1, P2 = 0)		**2138**	[redacted]
OS FP models, proportional hazards: 2nd order fractional polynomial model (P1 = 1, P2 = 1)		2140	[redacted]

Note: Best fitting models in bold. **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **OS**, overall survival; **PFS**, PFS; **FP**, fractional polynomial; **DIC**, Deviance Information Criterion; **ICER**, incremental cost-effectiveness ratio; **MSM**, multi-state Markov

A16. Please supply heterogeneity statistics for the fixed-effect constant HRs NMAs presented in section B.2.9.

Because the fixed-effects model assumes that differences in effect size between studies are due to sampling rather than true differences in the study populations, a heterogeneity statistic cannot be calculated. Instead, heterogeneity is calculated in the random effects model. This value (represented by the standard deviation reported in the footer of Table 43 and Table 44) is provided in response to question A17.

A17. **Priority question:** We acknowledge the statement that a fixed-effect NMA was done rather than a random-effects NMA due to the sparseness of the network, and the wide credible intervals for the heterogeneity parameter (as stated in Appendix D.1.1.5, page 35). For transparency and comparison purposes please supply the random effects constant HRs NMA results for both OS and PFS.

Results of the random effects NMA (presented as hazard ratios between all competing interventions along with 95% credible intervals) based on reported hazard ratios are presented in Table 43 (OS) and Table 44 (PFS).

The network of evidence contains 5 connections between 5 treatments. Each connection is informed by only one trial except for the MPT vs. MP comparison which is informed by two trials. The estimated hazard ratios were not stable given that the available data is too limited to estimate the between-study heterogeneity.[3] This results in wide credible intervals for the expected hazard ratios.

Table 43: Results of random effects NMA of OS based on reported constant hazard ratios

MP	1.59 (0.08, 30.99)	2.05 (0.01, 365.39)	2.07 (0.01, 348.20)	1.44 (0.02, 89.61)
0.63 (0.03, 12.49)	**MPT**	1.29 (0.02, 86.21)	1.30 (0.02, 89.21)	0.90 (0.01, 158.03)
0.49 (0.00, 87.79)	0.78 (0.01, 53.51)	**Rd**	1.01 (0.01, 66.01)	0.70 (0.00, 543.25)
0.48 (0.00, 85.92)	0.77 (0.01, 53.10)	0.99 (0.02, 66.95)	**Rd18**	0.69 (0.00, 542.30)
0.70 (0.01, 47.42)	1.11 (0.01, 198.10)	1.42 (0.00, 1122.00)	1.45 (0.00, 1091.02)	**VMP**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level. DIC: 8.96; Deviance: 4.13; SD: 1.26.
Key: Rd, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone.

Table 44: Results of random effects NMA of PFS based on reported constant hazard ratios; EMA-censored FIRST data

MP	1.79 (0.10, 32.08)	2.42 (0.02, 402.16)	1.74 (0.01, 294.56)	1.79 (0.03, 113.37)
0.56 (0.03, 10.26)	**MPT**	1.35 (0.02, 84.96)	0.97 (0.02, 65.45)	1.01 (0.01, 154.98)
0.41 (0.00, 60.92)	0.74 (0.01, 41.73)	**Rd**	0.72 (0.01, 43.84)	0.74 (0.00, 520.85)
0.58 (0.00, 83.35)	1.03 (0.02, 62.46)	1.39 (0.02, 89.19)	**Rd18**	1.03 (0.00, 672.96)
0.56 (0.01, 37.29)	0.99 (0.01, 171.30)	1.35 (0.00, 1048.02)	0.97 (0.00, 771.34)	**VMP**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level. DIC: 9.07; Deviance: 4.2; SD: 1.26.
Key: Rd, lenalidomide and low-dose dexamethasone until disease progression; **Rd18**, lenalidomide and low-dose dexamethasone for 72 weeks; **MPT**, melphalan, prednisone and thalidomide; **VMP**, bortezomib, melphalan, and prednisone; **MP**, melphalan, and prednisone.

A18. Table 13 in Appendix D.1.3 contains a quality assessment for Facon 2006 (IFM-95/01). However, this trial also appears in Table 59 of Appendix D, which lists excluded studies. Please confirm whether or not this trial should have been quality assessed as an included study.

This trial was not included in the network of evidence and should not have been quality assessed. The company apologises for this oversight.

Section B: Clarification on cost-effectiveness data

B1. On page 101, Document B, it is stated that patients who died or were censored for OS prior to 92 weeks were not included in the MSM analysis. Please state how many patients this applied to.

For Rd, 121 patients were censored or died before 92 weeks, and for MPT, 153 patients were censored or died before 92 weeks.

B2. The weighted costs per model cycle shown in Table 36, Document B, differs from the values in the economic model in worksheet Drug Costs. Please clarify which values are correct.

The weighted costs per model cycle presented in the "Drug Costs" worksheet in the economic model (S33:S56) are calculated based on mean RDI. However, the base case analysis calculates drug costs using individual patient data rather than the mean relative dose intensity (RDI), hence the correct weighted costs per cycle are found on the "Trial Dosing Costs" worksheet, cells X4:Z4. These provide the weighted cost per cycle before the patient access scheme (PAS) is applied.

However, the value provided in Table 36 in Document B is an error in the submission, and should be reported as [redacted] for lenalidomide, and [redacted] for dexamethasone, as per the model. The company apologises for this reporting error.

B3. The pack cost reported for melphalan and prednisolone in Table 35, Document B, differs from those reported in the economic model in worksheet Drug Costs. Please confirm which values are correct.

The value reported in the economic model for melphalan (Drug Costs I95) should be £45.38 per pack, and £26.19 for prednisolone (Drug Costs I97), as per the original company submission. The economic model submitted with the clarification responses includes this correction. However, it should be noted that this has not altered the ICER for Rd versus VMP, as this cell was linked to trial based dosing calculations for MPT only (L45). All drug cost calculations for melphalan and prednisolone are now solely linked to I95 and I97.

The "Drug Costs" worksheet in the updated Excel model has been adapted; cells J93, J95, I97, I95, L47 and L54 now link all drug costs to the same inputs.

B4. **Priority question:** Please provide a mapping of EORTC QLQ C30 data for the Rd and MPT groups to EQ-5D values for cycles 1-6 using the mapping algorithm by Proskorovsky et al.

The requested analysis has been conducted. Table 45 provides the EQ-5D utility values mapped from EORTC-QLQ-C30 data for Rd and MPT.

Table 45: Mapped EQ-5D values for Rd and MPT from the EORTC-QLQ-C30 data from MM-020

Cycle (per 4 weeks)	Mapped EQ-5D utility from EORTC-QLQ-C30 MM-020 data*	
	Rd	MPT
1	0.599 (823)	0.596 (546)
2	0.612 (154)	0.635 (385)
3	0.682 (232)	0.665 (208)
4	0.685 (185)	0.649 (195)
5	0.641 (44)	0.684 (53)
6	0.715 (162)	0.669 (109)

*Number of observations provided in brackets. **Key: Rd**, lenalidomide and low-dose dexamethasone until disease progression; **MPT**, melphalan, prednisone and thalidomide; **EORTC-QLQ-C30**, European organisation for research and treatment of cancer core quality of life questionnaire

Table 46 compares the differences in Rd and VMP utilities in cycles 1-6 used in the original company base case (Rd EQ-5D values from MM-020) and the EQ-5D values mapped from the EORTC-QLQ-C30 data (Table 45). For the latter, the VMP utility has been recalculated using the new baseline utility for Rd (0.599), to align the approach with the original company base case.

Per cycle, the differences between the two arms are highly comparable (Table 45). Moreover, the only discrepancy in the direction of the difference between arms occurs in cycle 5 when there are low numbers of observations in the Rd arm. Based on these results, we do not anticipate that using the mapped utility values for Rd would have a material impact on the cost-effectiveness of Rd, in comparison to the original company base case approach.

Table 46: Rd and VMP utilities

Cycle	Original company base case utilities			Mapped EQ-5D utility from EORTC-QLQ-C30 for Rd		
	Rd	VMP	Difference	Rd	VMP	Difference
1	0.52	0.54	-0.02	0.60	0.62	-0.02
2	0.56	0.53	0.03	0.61	0.61	0.01
3	0.56	0.52	0.04	0.68	0.60	0.09
4	0.63	0.55	0.08	0.69	0.63	0.06
5	0.63	0.59	0.04	0.64	0.67	-0.03
6	0.63	0.62	0.01	0.72	0.70	0.02

Key: Rd, lenalidomide and low-dose dexamethasone until disease progression; **VMP**, bortezomib, melphalan, and prednisone; **EORTC-QLQ-C30**, European organisation for research and treatment of cancer core quality of life questionnaire

B5. **Priority question**: The submission provides a scenario analysis of VMP vs. Rd using time-varying HRs using fractional polynomials (Table 52, Document B). Please conduct a one-way sensitivity analysis for this analysis using the upper and lower 95% credible interval values.

This sensitivity analysis was conducted exclusively for the parameters requested, and tornado diagrams are provided in Figure 14 and Figure 15, with the base case reflecting the

scenario where both OS and PFS use the best fitting time-varying hazard ratio model (an ICER of [redacted] and net monetary benefit (NMB) of [redacted] using a willingness-to-pay threshold of £30,000). Both ICER and NMB tornado plots have been shown due to the ICERs for the VMP OS d1 estimate reflecting bottom-left quadrant cost-effectiveness plane results.

It should be noted that these analyses do not (and cannot) correctly account for the inherent correlation between each of the input parameters for the time-varying HR, hence do not represent the associated uncertainty correctly. These results should therefore be treated with caution. Regardless, the only parameters that influence the overall decision were those relating to VMP OS, which aligns with the findings of the one-way sensitivity analysis (OWSA) presented in the original company submission.

The updated Excel model includes changes to the “Parameters” worksheet, where additional parameters have been added for the fractional polynomial inputs in rows 677:684.

Figure 14: One way sensitivity analysis (OWSA) results using 95% CrI for the time-varying hazards approach – ICER

Key: Rd, lenalidomide and low-dose dexamethasone until disease progression; **VMP**, bortezomib, melphalan, and prednisone; **PFS**, progression-free survival; **OS**, overall survival. **Notes:** Base case ICER is identical to the scenario using time-varying hazards for PFS and OS for Rd and VMP (£11,329). The ICER for the lower bound of the OS VMP d1 estimate lies in the lower left quartile of the cost-effectiveness analysis (CEA) plane, and therefore is not cost-effective.

Figure 15: OWSA results using 95% CrI for the time-varying hazards approach – NMB

Key: Rd, lenalidomide and low-dose dexamethasone until disease progression; **VMP**, bortezomib, melphalan, and prednisone; **PFS**, progression-free survival; **OS**, overall survival. **Notes:** Base case NMB is identical to the scenario using time-varying hazards for PFS and OS for Rd and VMP (£21,487).

B6. **Priority question:** Please clarify how you obtained the cost-effectiveness results for the scenario analysis: "Use TTP:PFS to extrapolate Rd and MPT DoT" (Table 52, Document B). Currently, choosing the option of "TTP:PFS" from the drop down menu in cell "DoT.Choice" within **Sheet!TTF and KMs** in the Excel model gives an error in the cost-effectiveness results"

An agreement was reached on the clarification questions call (15 November 2017) that a response to this question is no longer required.

Section C: Textual clarifications and additional points

C1. The clinical study report for the FIRST trial (reference 43 in the submission) contains table headings in section 14, but there are no tables provided. Please supply these.

Please see Appendix 2 and Appendix 3 of the clarification response which present the following data tables for the 21 January 2016 data cut of the MM-020 study:

- Efficacy results (Appendix 2)
- Demographic and safety results (Appendix 3)

C2. Figure 21 (page 106, Document B), PFS (left hand panel) – should an MPT survival curve appear in this figure?

As stated in the Notes section of Figure 21 (page 106, Document B), the PFS HR for VMP versus MPT is 1. This means that the curves are identical, and the VMP curve currently overlays the MPT curve, which is why the MPT curve is not visible.

References:

1) Celgene Corporation. Lenalidomide (REVLIMID®). A phase III, randomized, open-label, 3-arm study to determine the efficacy and safety of lenalidomide (REVLIMID®) plus low-dose dexamethasone when given until progressive disease or for 18 four-week cycles versus the combination of melphalan, prednisone, and thalidomide given for 12 six-week cycles in patients with previously untreated multiple myeloma who are either 65 years of age or older or not candidates for stem cell transplantation (IFM 07-01). Clinical study report CC-5013-MM-020/IFM 07-01. 31 August 2016 (data cutoff: 21 January 2016).

2) Cocks K, Cohen D, Wisløff F, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-MY20) in assessing the quality of life of patients with multiple myeloma. Eur J Cancer. 2007;43(11):1670-1678.

3) Jansen JP Cope S. Meta-regression models to assess heterogeneity and inconsistency in network meta-analysis of survival outcomes. BMC Medical Research Methodology 2012, 12:152.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Lenalidomide for previously untreated multiple myeloma [ID474]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Leukaemia CARE

Your position in the organisation: [redacted]

Brief description of the organisation:

Leukaemia CARE is a national charity which exists to provide vital support services to anybody affected by a diagnosis of blood cancer (or any allied blood disorder). This includes all types of leukaemia, lymphoma; multiple myeloma; myelodysplastic syndrome (MDS); myeloproliferative neoplasms (MPN) & aplastic anaemia.

Leukaemia CARE was founded in 1967 and first registered with the charity commission in 1969. Our current membership database stands at approximately 13,500 (this includes patients, carers and members of the patients' immediate family members.)

Leukaemia CARE offers this support through our head office, based in Worcester and a network of volunteers all around the United Kingdom.

Support is offered over seven key areas:

- 24-hour CARE Line and live chat (currently office hours only)
- Support groups
- Patient and carer conferences
- Nurse conferences
- One-to-one phone buddy support
- Cancer campaigning and patient advocacy
- Information and booklets

Since its inception over 25 years ago our CARE-Line has taken many thousands of calls from patients, their carers, family and friends. Our website provides extensive information on all aspects of the blood cancer journey, running from diagnosis to what happens when treatment stops and includes information on the emotional impact of a blood cancer and help for those caring for a patient. Our focus is purely on supporting anybody affected by a diagnosis of blood cancer, simply supporting a quality of life for all (see http://www.leukaemiacare.org.uk).

Leukaemia CARE also works with other charities and policy/decision makers to campaign for the rights of all patients affected by a cancer of the blood to have access to and receive the best possible treatment and care when they need it.

Organisational Funding:

Over 85% of our total funding comes from our own fund raising activities, either via our members and fund raisers, legacies, grants, on-line shop, Christmas card sales, recycling exercises etc.

Leukaemia CARE receives funds from a wide range of Pharmaceutical companies, but in total those funds do not exceed more than 15% of our total income. The funds received from the Pharmaceutical Industry are received and dispersed strictly within the Guidelines as laid down by the ABPI Code of Practice 2015, Clause 27 - Relationships with Patient Organisations.[1]

We also operate strictly within the Guidelines defined by the "Leukaemia CARE Code of Practice."[2] This Code of Practice governing corporate funding is a commitment undertaken by Leukaemia CARE regarding our financial relationships with commercial entities and the pharmaceutical industry in particular. Both of these documents can be examined via the hyperlinks listed below, or they are available in hard copy upon request.

We pride ourselves on our independence from any external influence/undue pressure arising from any of the other stakeholder bodies operating within the same sphere of activity as ourselves – the Industry, the NHS, the DoH, NICE, the Medical Profession etc., all bodies that we work closely with but are independent from. We will maintain our independence to the best of our ability and eschew any support that could adversely impact our reputation. This fact is made clear to any drug company (or other body) seeking our advice/assistance at the time of first contact. Our Code of Practice is also shared with them at that time.

1 - http://www.pmcpa.org.uk/thecode/InteractiveCode2015/Pages/clause27.aspx
2 - http://www.leukaemiacare.org.uk/code-of-practice

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Myeloma (also known as multiple myeloma) is a rare, incurable, relapsing, remitting and relentless cancer which affects the plasma cells. Plasma cells are a type of white blood cell found in the bone marrow which produce antibodies called 'immunoglobulins' to help fight infections. Normally new plasma cells are produced to replace old cells, but in patients with myeloma, abnormal amounts of plasma cells are produced which only produce one type of antibody called 'paraprotein', which has no useful function and cannot fight infection effectively.

The most common symptom of myeloma is severe bone pain. This frequently occurs in the lower back and can be very disabling, meaning that patients' quality of life can be vastly reduced. Myeloma affects multiple places in the body (hence 'multiple' myeloma) where bone marrow is normally active in an adult i.e. within the bones of the spine, skull, pelvis, the rib cage, long bones of the arms and legs and the areas around the shoulders and hips.

Other common symptoms include:

1. Loss of appetite, feeling sick and constipation
2. Tiredness and lethargy
3. Weight loss
4. Unusual bruising and or bleeding
5. Frequent and persistent infections
6. Kidney problems

Collectively these symptoms can substantially impact on patients' quality of life. Myeloma patients experience a number of relapses and remissions, which require effective treatment at each stage. The relapsing nature of myeloma can have a major impact on the physical and psychological wellbeing of patients and their carers, family and friends.

The majority of myeloma patients are over the age of 60, which may produce a range of complications and co-morbidities. Its multiple, complex mechanisms of action and this range of co-morbidities set it apart from almost every other cancer.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

The most important considerations from the patient perspective will include survival (both overall and progression-free) and a better quality of life.

It is important to note that for many patients an improvement in quality of life is often considered to be as important to patients as improved survival (i.e. quality may be as important as quantity).

Other key aims of treatment would include improved response rates and a reduction in the side effects of treatment.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

For newly diagnosed patients who are ineligible for ASCT, common first-line treatment options would include:

- Thalidomide (with an alkylating agent and a corticosteroid)
- Bortezomib (with an alkylating agent and a corticosteroid)

Bortezomib is rarely used in myeloma as a first-line treatment, unless people are unable to tolerate or have contraindications to thalidomide. As such, the most appropriate comparator treatment in this setting will be thalidomide.

However, it is important to note that there will be a group of patients who are unable to tolerate or are contraindicated to thalidomide who will be likely to receive bortezomib. Additionally, there will also be a group of patients who are unable to tolerate or are contraindicated to both thalidomide and bortezomib, for whom there are currently very limited treatment options.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health

- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

The key benefits that are expected include:

- Improved survival (both progression-free and overall)
- Improved quality of life
- Improved response rates
- Reduction in serious (grade 3 or 4) adverse events
- Oral treatment (ease of use)

As outlined above, these are important considerations for patients, for whom lenalidomide at first-line could have huge benefits.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

See above.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

N/A – We are not aware of any differences in opinion.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might

be willing to accept or tolerate and which would be difficult to accept or tolerate)

- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Please list any concerns patients or carers have about the treatment being appraised.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

N/A – We are not aware of any differences of opinion.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment

as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

We would like to draw attention to potential equality issues arising due to the nature of myeloma:

- Myeloma incidence is strongly related to increasing age.
- Myeloma disproportionately affects males.
- Myeloma disproportionately affects the black populations, and within that, particularly men.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Myeloma is a rare, incurable, relapsing, remitting and relentless cancer.
- Myeloma patients may experience a range of symptoms including – bone pain, tiredness, unexplained weight loss, frequent and persistent infections etc. These symptoms can collectively and individually impact hugely on patients' quality of life.
- For the small group of patients who are unable to tolerate or have contraindications to both thalidomide and bortezomib, there are currently very limited options.
- Lenalidomide appears to offer patients an improvement in progression-free survival; overall survival; response rates and quality of life.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Lenalidomide in combination with dexamethasone for previously untreated multiple myeloma [ID474]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Myeloma UK
3. Job title or position	Head of Patient Advocacy
4a. Brief description of the organisation (including who funds it). How many members does it have?	Myeloma UK is the only organisation in the UK dealing exclusively with myeloma. Our broad and innovative range of services cover every aspect of myeloma from providing information and support, to improving standards of treatment and care through research and campaigning. We receive no government funding and rely entirely on the fundraising efforts of our supporters and unrestricted educational grants from a range of pharmaceutical companies.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information included in this submission has been gathered from the myeloma patients and carers we engage with through our research and services programmes, including: • Telephone and face-to-face interviews with myeloma patients about their expectations of treatment, and their thoughts on the myeloma treatment pathway • A Myeloma UK patient experience survey of over 1,000 patients, conducted alongside the myeloma results of the National Cancer Patient Experience Survey • A multi-criteria decision analysis study of 560 myeloma patients funded by Myeloma UK and run by the European Medicines Agency (EMA) and University of Groningen which explored patient preferences for different benefit and risk outcomes in myeloma treatment It has also been informed by analysis of the experiences and views of patients, family members and carers gathered via our Myeloma Infoline, Patient and Family Myeloma Infodays and posts to our online Discussion Forum.

	This provides a comprehensive and in-depth picture of the experience, needs and priorities of people affected by myeloma.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**What is it like to live with myeloma?** *"Myeloma creeps up on you, engulfs you and, if you win the battle, leaves you wondering when it will come back."* Myeloma is a highly individual and complex cancer originating from abnormal plasma cells in the bone marrow. There is currently no cure, but treatment can halt its progress and improve quality of life. Myeloma is also a relapsing and remitting cancer which evolves over time and becomes resistant to treatment. Patients experience an increasing sense of despair when they relapse and are faced with limited treatment options. The complications of myeloma can be significant, debilitating and painful and include: severe bone pain, bone destruction, kidney damage, fatigue and a depleted immune system. Myeloma patients are more likely to be diagnosed late and often present in secondary care with bone lesions, fractures and, in the worst cases, collapsed vertebrae. This compounds the distress of their diagnosis and impacts negatively on pain levels, mobility and their ability to complete everyday tasks. Treatment side-effects and frequent hospital visits have a social and practical impact on patients' lives, including significant financial implications. Reduction in mobility over time and a perceived increase in reliance on carers and family members, also impacts on patients' sense of control. However, many myeloma patients, including those who are multiply relapsed, can have durable and deep responses to treatment and good quality of life – but only if they have access to new, effective and

	innovative treatments. There is therefore an urgent and continual need for new treatments to ensure that patient survival rates keep improving. **What do carers experience?** *"I feel angry that I'm not going to get the future I wanted, but the hardest thing to feel is how my life at the moment is in limbo"* A recent Myeloma UK study[1] into the experiences of carers and family members found that looking after someone with myeloma has a significant emotional, social and practical impact. Carers' lives can change dramatically because of their caring responsibilities: 25 per cent of those in work had been unable to work or had to retire early to care for the person with myeloma. They often carry a heavy emotional burden with 84 per cent always putting the needs of their relative or friend with myeloma before their own. The impact of myeloma on the well-being of carers is also often overlooked; 42 per cent of carers were not given enough information at diagnosis about how myeloma may affect them Living with myeloma is therefore often extremely challenging physically and emotionally for patients, carers and family members.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	**What treatment outcomes are important to myeloma patients?** We know from our programmes of engagement that myeloma patients and their carers place a very high value on treatments that put their myeloma into remission for as long as possible, prolong their life and allow them to enjoy normal day-to-day life. To expand on this: • In the joint Myeloma UK, EMA, University of Groningen study, the majority of patients considered progression free survival (PFS) to be the most important attribute to consider when making a

[1] The study, conducted between May and June 2016, was designed with the input of carers and involved a survey of 374 carers and a second stage of interviews to explore issues in more depth.

decision on a new treatment.

- Treatments with minimal negative impact on quality of life are very important, particularly those with as few side-effects as possible and of low severity. "*The aim is to maintain the best possible quality of life for as long as possible."*
- As myeloma is a highly individual, relapsing and remitting cancer which becomes resistant to treatment, patients need and want a range of effective treatment options; treatments with different mechanisms of action, administered in a range of ways, at every stage of the treatment pathway
- Again, due to its relapsing and remitting nature, patients do not see the survival benefits of individual treatments in isolation; gains in survival from one treatment are seen as a "bridge" to further treatments coming down the line. *"A drug like this can be a gateway to other treatments that can extend your life even further"*

What do patients think of current treatment and care?

Currently, newly diagnosed myeloma patients ineligible for HDT-SCT can receive either a thalidomide-based regimen or bortezomib (Velcade®) (if they are intolerant/contraindicated to thalidomide). Thalidomide and bortezomib are generally well tolerated by myeloma patients and can prolong survival.

However, some patients report that a number of the side-effects of these treatments are difficult to deal with and can be debilitating. Both treatments are associated with peripheral neuropathy (which affects up to 30% of patients receiving bortezomib). This can range from mild and temporary tingling in hands and feet, through to permanent shooting pains requiring significant supportive care and pain relief.

> *"I have permanent damage in my extremities, my feet constantly feel icy and like they don't belong to my body – when I touch between my knees and feet I can't really feel anything. It is because of this I trip up all of the time."*

	"It can only be described as a feeling of walking on rocks. I had a constant burning sensation in my hands and feet, which got much worse at night and meant I struggled to sleep. This combined with having terrible fatigue related to my myeloma, meant that it impacted on my ability to do things." Bortezomib is the alternative treatment option for patients who cannot have thalidomide, but this may not always be appropriate for patients who are older and/or frailer (who have a higher susceptibility to side-effects) or for patients who cannot tolerate bortezomib due to peripheral neuropathy (either pre-existing or drug related). If patients have pre-existing neuropathy, or have developed neuropathy through exposure to thalidomide, an alternative treatment is needed. If patients were able to access lenalidomide, it could potentially stop further damage and also prevent permanent damage to nerves. Administering bortezomib subcutaneously has reduced the impact of peripheral neuropathy but this can bring further challenges, particularly for elderly and frail patients. Patients have to attend hospital in order to receive treatment, which can be difficult for patients with mobility problems and also requires all patients to take the time out of their daily routine to attend day clinics. In some circumstances patients are content to attend hospital in order to achieve a good outcome and some patients like the "safety" and sense of community found in day clinics. However, most patients welcome the option of an oral regimen.
8. Is there an unmet need for patients with this condition?	Yes. The individual and heterogeneous nature of myeloma means that some patients may tolerate a treatment well and others may not. In addition myeloma evolves and becomes resistant to treatment. It is therefore essential to have a range of treatment options with different mechanisms of action at all stages of the myeloma pathway. "*To say, "Well you already have a treatment." That's not good enough. You always have to show myeloma something new."*

	In addition, for the reasons outlined at point 7, above, some patients who cannot receive thalidomide are also not suitable for treatment with bortezomib. Therefore, there is a particular unmet need for patients who are not suitable for treatment with thalidomide and for whom existing treatment options are limited and sometimes undesirable since they are challenging to deliver and increase the risk of reducing quality of life.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Data from the MM - 020 FIRST trial shows that lenalidomide prolongs progression free survival (PFS) and overall survival (OS) in newly diagnosed myeloma patients. These are outcomes we know myeloma patients value greatly. In addition, evidence suggests that patients who attain a good response from their initial treatment have better long term outcomes. Lenalidomide provides doctors with a further front-line option to deliver maximum depth and duration of response. Furthermore, lenalidomide is an innovative treatment, with a different mechanism of action to thalidomide, and its tolerability means that it can be given continuously until disease progression, helping to extend remission. The reduced side effect profile of lenalidomide, particularly the reduced incidence of peripheral neuropathy, is also highly valued by patients. Revlimid is also likely to be given in a two-drug rather than three drug combination, which is particularly beneficial to older/frailer patients. The oral regimen is easy to take and enables patients to have more control over their lives. Myeloma patients who are ineligible to receive HDT-SCT, can often perceive that they are receiving less effective treatment. It is very important therefore for patients and their families to know that the FIRST® trial has shown that patients in the non-intensive pathway can have a near equivalent response to those

	patients undergoing HDT-SCT, providing much needed reassurance that they are receiving the best possible treatment regardless of their age or fitness.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Side-effects of Revlimid include low blood counts and there is a risk of venous thromboembolism and blood clots whilst taking the treatment. Patients also frequently report fatigue which impacts negatively on their quality of life and peripheral neuropathy, although this is a lesser risk than in thalidomide and Velcade. Another side-effect is skin rashes. As with other treatments these side-effects can be largely mitigated or improved through appropriate management by a healthcare professional. Revlimid is also given on a treat until progression basis, so patients do not have long treatment free breaks.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Frail and elderly patients who are more susceptible to side-effects, potentially less able to travel to receive treatment, and who would benefit from a two drug rather than a three drug combination.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No.
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	

15. In up to 5 bullet points, please summarise the key messages of your submission:

- There is an unmet need for treatments with a different mechanism of action and reduced side effect profile for newly diagnosed myeloma patients. Lenalidomide is an innovative and effective treatment to add to the myeloma treatment pathway for patients who are ineligible for HDT-SCT. Approving lenalidomide in this setting significantly improves treatment options for this group of patients, enabling doctors to personalise treatment and choose the option best suited to the clinical situation.

- Lenalidomide can substantially increase progression free and overall survival; outcomes which are valued highly by patients
- Lenalidomide gives patients the opportunity to achieve a deeper response at first treatment which is beneficial to long-term survival
- It offers patients improved quality of life through its reduced side effect profile and by treating the underlying disease and reducing symptoms, helping patients to lead enjoyable, fulfilling and productive lives. This also lessens the burden on carers and family members.
- Its oral formulation is welcomed by patients, giving them more control over their day to day lives. The oral regimen is especially helpful to older frailer patients who will also derive particular benefit from its reduced side effect profile and the fact it is given in a two drug combination.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Lenalidomide in combination with dexamethasone for previously untreated multiple myeloma [ID474]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Uk Myeloma Forum**

3. Job title or position	**Consultant Haematologist** [redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	UK myeloma forum is the only UK organisation that represents Physicians, Nursing staff, Pharmacists and Healthcare professionals who are directly involved with providing clinical care or research for patients with myeloma. Membership is free by application and members of the executive board are elected by the membership. It aims to improve the care of myeloma patients through the development and promotion of trials and best practice, providing education about both the disease and its management to healthcare professionals. Funding is derived from charitable donations, educational meeting attendance fees and donations from Pharmaceutical company sponsors
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to	Myeloma is currently incurable. Most people diagnosed with myeloma die as a result of complications of the disease. Symptoms and signs include bone pain, fractures secondary to bone deposits, anaemia (fatigue, shortness of breath, chest tightness), recurrent infections, renal failure, high calcium levels and

stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	occasionally spinal cord compression. Treatment is primarily aimed at reducing or preventing these symptoms by controlling the disease. There is a direct association between improvement in quality of life and how well the underlying disease is controlled i.e. A complete remission being better than partial response. A primary aim of treatment is to maintain this control (and thereby symptoms) for as long as possible (i.e. lengthen the progression free survival / duration of response), lengthen life (i.e. increase overall survival) and prevent significant morbidity associated with progression of the disease.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	There are international agreed criteria for assessing response (International Myeloma Working Group Rajkumar et al. Blood 2011;117:4691-4695 These are based on the proportional reduction on serum paraprotein / serum free light chains (serological markers of myeloma) or urine monoclonal protein + bone marrow proportion of myeloma plasma cells. Generally, a Partial Response (PR) or better is considered clinically significant. Increasingly with more efficacious treatments the aim of the therapy is to achieve Complete Response (CR) or Very Good Partial Response (VGPR) for as many patients as possible. It is apparent in many studies that the greater the depth of response the longer the duration of the response (CR>VGPR>PR). There is also an association between CR and longer overall survival.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. This is a disease that is incurable with current therapy for all but a minority of patients. First line therapy should be aimed at achieving the highest and deepest possible response rates with the longest / most durable responses thereby reducing both the morbidity and mortality associated with the disease. Ideally this is achieved with a well tolerated and oral treatment combination. Currently available first line therapies for non-transplant eligible patients are reported as less effective (e.g. cyclophosphamide /thalidomide/dexamethasone;CTD) or require regular attendance at hospitals for sub-cutaneous (S/C) treatment administration (e.g Velcade /melphalan/prednisolone; VMP).
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guideline TA229 recommends alkylator therapy + thalidomide + steroid (CTD or MPT) as 1st line therapy for non-transplant eligible patients unless thalidomide intolerant or contraindicated, in which case bortezomib + alkylator + steroid is recommended (VMP). NHSE approved funding support for VMP in 2013 as baseline commissioning although it is reported to be not available in all areas i.e. there is variable access to VMP. NICE declined to review the TA229 guidance in 2016. European Society of Medical Oncology Guidelines 2017 (Annals of Oncology 28 (suppl 4) iv 52-61 recommends VMP or Rd (lenalidomide / dexamethasone) for 1st line therapy.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined. Patients are assessed according to autologous transplant eligibility and then treated on non-transplant eligible or transplant eligible pathways. Whilst it is generally accepted that VMP has been the treatment combination regimen that is associated with the best response rates, longest responses and improvements in overall survival it is not accessible in all localities. It is also recognised that it is potentially less deliverable than all oral combinations (e.g CTD /MPT or Lenalidomide / dexamethasone (Rd)) which means that a significant proportion of patients receive CTD. Generally in the UK for those receiving thalidomide based treatment CTD is used in preference to MPT as this was one of the arms of the Myeloma IX trial (Morgan et al. Blood 2011;118(5):1231-1238) that influenced clinical practice significantly.
• What impact would the technology have on the current pathway of care?	This is an effective well tolerated all oral treatment combination. There would be a significant improvement in durable control of the disease with associated improvements on quality of life. It is also well tolerated with minimal side effects and compliance is likely to be good. For patients particularly if they live a long distance from their treatment unit the reduction in the number of attendances and the associated reduction in healthcare resource utilisation (HRU), especially that associated with S/C administration of velcade would be welcomed.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	

• How does healthcare resource use differ between the technology and current care?	Yes – it would substitute for CTD/MPT. There are no differences in healthcare resource required for Rd
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil. The combination is currently used at 3rd line and beyond and there is extensive UK experience already.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	The progression free survival for the continuous Rd treatment arm in the MM-020 trial (Benboubker et al NEJM 2014;371:906-17), which formed the basis of the evidence for the EMA submission and approval, is significantly superior to the control treatment (MPT) and with short follow-up (median 37 months) there is a small but significant improvement in overall survival for continuous Rd treated patients (59% at 4 years HR 0.78 p=0.02) which is likely to increase with extended follow-up. In Real World use it is likely to improve overall survival.

• Do you expect the technology to increase health-related quality of life more than current care?	Yes. This is a well tolerated oral regiment with limited side effect profile compared with both CTD/MPT and VMP. It has the advantage that it only required monthly attendance at the administration centre.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Easier than VMP (as less regular hospital attendance required). The main difference compared with CTD/MPT oral regimens is a much lower rate of peripheral neuropathy resulting in better quality of life. The main concomitant medication required is the use of aspirin or low molecular weight heparin to reduce the thrombosis risk (this is also required for thalidomide based treatments).

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes. Quality of life likely to be improved due to reduced myeloma associated complications, less hospital attendance and ease of administration.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial	

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes. This is an effective all oral treatment
• Does the use of the technology address any particular unmet need of the patient population?	No
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effect profile for Rd is generally less extensive than that for CTD / MPT or VMP this includes the risk for peripheral neuropathy which a common dose and treatment limiting side effect for thalidomide / bortezomib. There is a moderate increase in reported infections, thromboembolic events and cardiac events with Rd compared with MPT in the MM—020 trial.
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	The 2 most commonly used regimens for non-transplant eligible patients are CTD (Morgan et al. Blood 2011;118(5):1231-1238) and VMP (San Miguel et al NEJM 2008;359:906-17; San Miguel et al J Clin Onc 2012;31:448-455). MPT (the comparator in MM-020 trial) is considered relatively equivalent to CTD. A meta-analysis of 6 clinical trials using MPT has been described (Fayers et al. Blood 2011 118(5);1239-1247). All of these clinical trials used the same control arm / comparator: Melphalan / Prednisolone (MP). This allows some extrapolation for cross comparison. The MM-020 trial used MPT as the control treatment (Benboubker et al NEJM 2014;371:906-17) as this was considered the international standard for an all oral therapy.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall response rate including CR, progression free survival, overall survival and adverse events profile
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	CR rate and Progression free survival are considered good predictors of overall survival in myeloma trials for non-transplant eligible patients.

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	No

21. How do data on real-world experience compare with the trial data?	There is limited experience with Real World Rd for 1st line patients. However, there is an enormous experience with using the combination for relapsed disease. Response rates, durations of response and tolerability have exceeded expectations based on the phase 3 trials for relapsed myeloma.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
22b. Consider whether these issues are different from issues with current care and why.	no
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains	

uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Rd is efficacious and well tolerated. It has the best outcomes for any all oral treatment regimen for newly diagnosed myeloma
- This combination should be made available to allow patient choice for 1st line therapy
- Current NICE guidance for 1st line therapy requires updating to reflect treatment that is considered current best practice
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Lenalidomide for previously untreated multiple myeloma [ID474]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Karthik Ramasamy**
2. Name of organisation	**Oxford University Hospitals NHS Trust**

3. Job title or position	**Consultant Haematologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To enhance survival and limit disease related morbidity and improve poor quality of life
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Partial response or better
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, disease remains incurable
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Thalidomide based or Bortezomib based therapy
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidance NG35
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes
• What impact would the technology have on the current pathway of care?	By moving this to newly diagnosed setting, second relapse option will be primarily Bortezomib / dex/ Panobinostat based
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes

• How does healthcare resource use differ between the technology and current care?	This is oral and therefore easier to deliver than Bortezomib, which is current standard of care. This is better tolerated than Thalidomide which is an oral option for these patients
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil required
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the	Yes

technology to increase health-related quality of life more than current care?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No particular sub groups have been identified in the trial (MM020)
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	Would be much easier to deliver as since 2009 this therapy was given to second relapse patients. The system is primed to deliver this therapy and would free up NHS resources (day therapy) for patients who currently receive Bortezomib

or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Newly diagnosed MM and not eligible for transplant (Start rule) Progression, side effects or death (stop rule)
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, due to longer remission periods and better tolerability
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	Yes, ability to deliver continuous therapy has not been feasible previously

benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Ability to receive continuous therapy and be able to deliver therapy for patients with neuropathy
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects are manageable and physician learning from using this combination in relapse will come in handy
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	PFS and OS
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator	No

treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	
22. How do data on real-world experience compare with the trial data?	Similar results have been obtained in UK MMXI trial. We have no RWE of using this agent outside of trials
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Patients in Scotland and Wales receive this drug in newly diagnosed setting
23b. Consider whether these issues are different from issues with current care and why.	
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Oral therapy
- Well tolerated and therefore be able to deliver continuously
- Improved PFS and OS
- Ability to treat elderly > 75 year age group
- Ability to treat patients with neuropathy

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Lenalidomide for previously untreated multiple myeloma [ID474]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr. Matthew Streetly**
2. Name of organisation	**UK Myeloma Forum / Guys and St. Thomas' NHS Foundation Trust**

3. Job title or position	**Advocacy Lead UKMF / Consultant Haematologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	

• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	

• Do you expect the technology to increase health-related quality of life more than current care?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
20. Are you aware of any relevant evidence that might	

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	
22. How do data on real-world experience compare with the trial data?	
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	

23b. Consider whether these issues are different from issues with current care and why.	

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

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Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Lenalidomide in combination with dexamethasone for previously untreated multiple myeloma

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Dr Keith Cooper, Senior Research Fellow (Health Economics)
Ms Neelam Kalita, Research Fellow (Health Economics)
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Declared competing interests of the authors

None from the authors. Dr Jenner has received honoraria to given educational presentations about myeloma within licensed indications, particularly high risk transplant eligible myeloma from Janssen (manufacturer of bortezomib) and has received sponsorship to attend American Society of Hematology Annual Meeting December 2017, Atlanta USA from Janssen. Dr Jenner has also received honoraria to chair educational meeting about myeloma within current licensed indications from Celgene (manufacturer of lenalidomide). Dr Jenner is a co-chief investigator on MUK nine b clinical trial evaluating lenalidomide, bortezomib and daratumumab combinations in newly diagnosed high risk transplant eligible myeloma and is a member of the Myeloma XI Trials Management committee which includes lenalidomide and bortezomib in newly diagnosed myeloma (all ages). Professor Yong has received research funding from Celgene to carry out a survivorship and exercise study for myeloma patients (study now closed). Dr Bird has chaired an educational meeting in Bristol on behalf of Celgene in October 2016.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

Keith Cooper critically appraised the health economic review, critically appraised the economic evaluation, and drafted the report; Neelam Kalita critically appraised the health economic review, critically appraised the economic evaluation, and drafted the report; Petra Harris critically appraised the clinical effectiveness review and drafted the report; Wendy Gaisford critically appraised the clinical effectiveness review and drafted the report; Jonathan Shepherd critically appraised the clinical effectiveness review, drafted the report, project managed the assessment and is the project guarantor.

Word count:

40,922

[redacted]

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Akaike information criteria
AMT	Anti-myeloma therapy
BIC	Bayesian information criteria
BOR	bortezomib
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
CRD	Centre for reviews and dissemination
CTDa	Attenuated cyclophosphamide, thalidomide and dexamethasone
CVD	Cyclophosphamide, bortezomib and dexamethasone
DEX	dexamethasone
DIC	Deviance Information Criteria
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC Quality of Life Questionnaire – Core 30
EORTC QLQ-MY20	EORTC Quality of Life Questionnaire – Multiple Myeloma 20
EQ-5D	European Quality of Life questionnaire-5 dimension
ERG	Evidence review group
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FP	Fractional polynomial
GCSF	Granulocyte-colony stimulating factor
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IFM	Intergroupe Francophone du Myelome
IRAC	Independent response adjudication committee
ISS	International staging system
ITT	Intention-to-treat
KM	Kaplan-Meier
MID	Minimal important difference
MIMS	Monthly Index of Medical Specialities
MM	Multiple myeloma
MP	Melphalan and prednisone
MPT	Melphalan, prednisone and thalidomide
MSM	Multi-state Markov
NDMM	Newly diagnosed multiple myeloma
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NMA	Network meta-analysis

ORR	Overall response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease
PICO	Patient intervention comparison outcome
PFS	Progression free survival
PFS2	Progression free survival 2
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
Rd	Lenalidomide and dexamethasone (continuous)
Rd18	18 cycles of lenalidomide and low-dose dexamethasone
SAE	Serious adverse event
SD	Stable disease
Sd	Standard deviation
SLR	Systematic literature review
SmPC	Summary of Product characteristics
TEAE	Treatment-emergent adverse event
TNT	Time to next treatment
TTP	Time to treatment progression
TTF	Time to treatment failure
UK	United Kingdom
VGPR	Very good partial response
VMP	Bortezomib, melphalan and prednisone

SUMMARY

The company submission (CS) presents evidence of the clinical effectiveness and cost effectiveness of lenalidomide (REVLIMID®) in combination with low-dose dexamethasone (Rd), for the first line treatment of patients with newly diagnosed multiple myeloma or untreated multiple myeloma. Lenalidomide is an oral therapy that provides an alternative treatment to current intravenous and subcutaneous therapies. Lenalidomide is a synthetic derivative of thalidomide given as a two drug combination with low-dose dexamethasone (Rd). The recommended starting dose is 25 mg/day to be taken orally for 21 days followed by a seven day rest period (28 day cycle), with treatment continued until disease progression or intolerance occurs.

The patient population in the CS is adults with previously untreated multiple myeloma for whom stem-cell transplantation is considered inappropriate. The CS reports a comparison of the effects of Rd versus melphalan, prednisone and thalidomide (MPT) and for people who are unable to tolerate, or have contraindications to thalidomide, Rd versus bortezomib, melphalan and prednisone (VMP). The CS does not include an alternative thalidomide combination therapy comprising attenuated cyclophosphamide, thalidomide and dexamethasone (CTDa) as it is not licensed in the UK. Expert advice to the ERG is that CTDa is widely used in the UK despite not being licensed and it can be considered comparable to MPT in effectiveness (both regimens contain thalidomide, a steroid and an oral chemotherapy agent). Expert clinical advice to the ERG also highlighted that other bortezomib regimens are used (less commonly) for first line treatment, e.g. bortezomib with cyclophosphamide, and dexamethasone (CVD). This regimen is not licensed for first line use in the UK and there does not appear to be much clinical trial evidence available to facilitate a comparison with lenalidomide.

Summary of submitted clinical effectiveness evidence

Systematic literature searches were performed to identify relevant clinical effectiveness studies. A total of four randomised controlled trials (RCTs) were included in the review, one RCT evaluated lenalidomide (termed MM-020 / FIRST) whilst the other three evaluated comparator treatments for inclusion in a network meta-analysis (NMA). MM-020 was an open-label three arm phase III RCT comparing the efficacy and safety of Rd, delivered either over 18 cycles (18 x 28 days: Rd18; n=541 patients) or continuously (for 21 out of 28 days) until disease progression (Rd; n=535) to MPT over 18 cycles (n=547). The trial was used to support the

marketing authorisation for lenalidomide for this indication and is a key source of evidence for the company's cost-effectiveness analysis.

The trial was carried out in 151 centres across the United Kingdom (n=72 UK patients), Europe, North and South America and Asia. The primary outcome measure was progression free survival (PFS). Secondary outcome measures included: overall survival (OS); time to treatment failure (TTF); time to progression (TTP); time to next treatment (TNT); tumour response (measured as complete response (CR); very good partial response (VGPR) or partial response (PR)); duration of response (DoR); time to second line anti-myeloma therapy (AMT), health related quality of life (HRQoL); adverse events (AEs) and PFS2. PFS2 was defined as "Time from randomisation to second objective progressed disease, start of third-line therapy or death from any cause, whichever occurred first" (CS page 41). Patient cross-over between trial arms was not permitted during the trial, however, upon disease progression patients in all arms received subsequent lines of treatment with either the same or an alternative anti-myeloma treatment.

Outcome data were collected at two time points; the 24th May 2013 (a planned final analysis of PFS and a planned interim analysis of OS) and the 21st Jan 2016 (planned final analysis of OS, and updated analysis of PFS). PFS, OS, TTF, HRQoL and AEs, obtained at the 21st Jan 2016 data cut-off, were used in the company's cost-effectiveness analysis.

Results of the MM-020 trial

We focus on the results of the continuous Rd arm of the trial compared to the MPT arm because the company's main analysis is for continuous (rather than fixed duration) lenalidomide compared to MPT or VMP. Final PFS obtained using the Independent Response Adjudication Committee (IRAC) review and the Food and Drugs Administration (FDA) censoring rules at the 24th May 2013 data cut-off showed a 28% reduction in the risk of disease progression or death with continuous Rd compared with MPT given for 72 weeks (Hazard ratio (HR) 0.72; 95% confidence interval (CI) 0.61–0.85; p=0.00006) with a difference of 4.3 months in median PFS between the groups (25.5 months Rd, 21.2 months MPT). At the 21st Jan 2016 data cut-off, Rd demonstrated a significant improvement of 10 months for median OS compared with MPT (HR 0.78; 95% CI 0.67–0.92; p=0.002).

The CS reports PFS and OS results for a range of subgroups including baseline International Staging System (ISS) disease stage, geographical location, sex and parameters of prognostic significance (e.g. baseline cytogenetic risk categories and baseline renal function). These pre-planned analyses, presented for the intention to treat (ITT) population at the 21st January 2016 data cut-off, demonstrated a PFS benefit in favour of Rd versus MPT in most subgroups.

The majority of patients (>99%) had at least one treatment-emergent adverse event (TEAE) regardless of treatment arm, occurring shortly after treatment initiation and decreasing in frequency over time. In the Rd treatment group, the most common TEAEs at any grade experienced in ≥10% of patients were diarrhoea (47.2%), anaemia (45.7%), constipation (44.2%) and peripheral oedema (41.2%). In the MPT group, AEs with the highest proportion of patients were recorded as neutropenia (60.6%), constipation (52.7%), anaemia (42.3%) and peripheral oedema (39.7%). Psychiatric disorders (described as including insomnia and depression) were reported to impact on nearly half of the patients in the Rd group compared to approximately a third for MPT (49.6% Rd; 30.9% MPT).

Grade 3-4 AEs affecting the greatest proportion of patients in the Rd group included anaemia (18.8%), neutropenia (29.5%) and vascular disorders (10.9%). In the MPT group common individual grade 3-4 AEs experienced by patients included neutropenia (44.9%) anaemia (18.9%) and thrombocytopenia (11.1%). The CS reports that Grade 3 or 4 AEs with Rd occurred slightly less frequently than with MPT (86.3% vs 88.7% of patients respectively) despite the longer duration of treatment.

Treatment discontinuations occurred largely as a result of disease progression, rather than as a result of TEAEs from Rd or MPT. Discontinuations due to TEAEs of lenalidomide or thalidomide occurred in over 25% of patients in both treatment groups (25.6% Rd and 27.0% MPT). Dose interruptions, however, were higher across treatment groups (68.0% Rd and 71.9% MPT) compared to dose reductions (41.4% Rd and 47.0% MPT). In summary, there appears to be no major safety concerns about treatment with Rd.

HRQoL data were collected using three questionnaires, the generic 5-dimension European Quality of Life questionnaire (EQ-5D) and six pre-selected and clinically relevant HRQoL domains from the European Organisation for Research and the Treatment of Cancer Quality of Life Questionnaire–Myeloma 20 (EORTC QLQ-MY20) and the general oncology-related

EORTC Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30). Patients completed questionnaires at several time points, at baseline and at the end of cycles 1, 3, 6, 12 and 18. As the regimens were identical over the 18-month measurement period, HRQoL data for the two Rd arms were combined into one overall group, post-hoc, for presentation of results. The ERG considers this to be acceptable in this instance.

Data show improved HRQoL with a number of statistically significant and clinically meaningful changes from baseline for both Rd and MPT. There were few statistically significant differences in HRQoL between the trial arms. Rd demonstrated statistical superiority to MPT in terms of impact of side effects on HRQoL. The ERG note that efficacy endpoint analyses were carried out using the ITT population, however it was not stated how missing response data or missing HRQoL data were estimated. This raises uncertainty in the interpretation of the HRQoL results.

Network meta-analysis (NMA)

No direct comparison of lenalidomide with bortezomib was identified in the systematic review; therefore a network meta-analysis (NMA) was conducted to compare the two drugs indirectly. The process for searching and screening studies for inclusion in the NMA was the same as used to identify studies of the clinical effectiveness of lenalidomide. Four RCTs were included in the network. One trial each for lenalidomide (MM-020) and bortezomib (VISTA) were included, whilst two trials of MPT (versus MP) were included. The company used two different statistical methods to conduct the NMA. One was a Bayesian NMA using constant hazard ratios (assuming proportional hazards). The other was a Bayesian time-varying hazard ratio NMA model using fractional polynomials. Both of these were conducted as “it was not known in advance which would provide the best combination of fit and parsimony” (CS page 67). The company subsequently chose the constant hazard ratios NMA as their primary (base case) analysis. The ERG agrees with this decision.

The CS assessed the methodological quality of the four RCTs included in NMA, using the Cochrane risk of bias criteria. Overall the studies appear to have been well conducted and the ERG mostly agreed with the company, however, for a number of domains the ERG’s judgement was that the risk of bias was unclear due to limitations in study reporting.

Results from the fixed effect NMA showed that patients treated with Rd had a lower risk of disease progression or death (PFS) compared with those who received MPT (HR 0.74; 95% (credible interval (CrI) 0.65 to 0.85), or VMP (HR 0.74; 95% CrI 0.52 to 1.05). The CS also presents PFS time-varying HRs under the best-fitting second order fractional polynomial NMA model. Results from this model indicate that the HR of Rd relative to MPT decreases over the course of follow-up (described in the CS as being statistically important (significant) at approximately 18 months). The credible intervals for the HR of VMP relative to MPT are wide and therefore very uncertain, particularly after 24 months.

Summary of submitted cost effectiveness evidence

The CS includes:

- A review of published economic evaluations of immunomodulatory drugs for adults with untreated newly diagnosed multiple myeloma who were ineligible for stem cell transplantation and/or older than 65 years of age.
- A report of an economic evaluation undertaken for the NICE STA process. The cost-effectiveness of Rd is compared with MPT and VMP.

A systematic search was conducted by the company to identify economic evaluations in patients with untreated newly diagnosed multiple myeloma who are ineligible for stem cell transplantation. Six publications corresponding to five economic studies were identified for full review. One study by Usmani et al. compared the cost-effectiveness of Rd versus VMP in transplant ineligible patients with newly diagnosed multiple myeloma from the US payer perspective. This study is most relevant to this appraisal because it compared lenalidomide with bortezomib. The study found Rd to be more cost-effective compared to VMP as it was associated with greater life years and quality adjusted life years (QALYs) with similar overall costs.

The company constructed a de novo cost-utility model to evaluate the cost-effectiveness of Rd with MPT and VMP. The model has cycles lasting four weeks and a lifetime horizon of 25 years. Costs and health benefits are discounted at 3.5% per annum, with a half-cycle correction applied. The model has three health states: progression-free, progressive disease and death.

The economic model uses clinical effectiveness evidence from the MM-020 trial to compare Rd and MPT. The NMA provides clinical effectiveness evidence for the comparison of Rd and VMP. The model uses the Kaplan-Meier data for PFS and OS from the trial for the first 92 weeks and

uses transition probabilities between health states thereafter. VMP was incorporated by applying a relative treatment effect from the NMA to the PFS and OS predictions generated for the multi-state Markov model for MPT. The mean hazard ratios for PFS and OS for VMP vs. MPT were 1.00 and 1.11 respectively.

Utility estimates were taken from the company's MM-020 trial for Rd and MPT, in which quality of life data from the EQ-5D questionnaire were collected. For VMP, European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) data from the VISTA trial (which compared VMP with MP) were mapped to EQ-5D using a published algorithm.

The average cost of a course of treatment of Rd is £[redacted] using the list price of lenalidomide. Lenalidomide is offered with a patient access scheme (PAS), whereby the company proposes to pay the cost of lenalidomide for any treatment beyond 26 cycles. They propose an adaptation to this where they will pay the cost of lenalidomide after [redacted] cycles (conditional on a positive recommendation from NICE). The cost effectiveness results reported in the CS (and in this ERG report) are for the [redacted] cycle cap, and the results based on the 26 cycle cap are reported in an appendix. The average cost of Rd including the PAS is £[redacted]. Thalidomide is an oral treatment taken for a maximum of 12 cycles of 42 days (72 weeks). Bortezomib is administered subcutaneously in the outpatient setting for nine cycles of 42 days each (54 weeks). The dosages and cost of comparator treatments are taken from the Monthly Index of Medical Specialities (MIMS). In the company's base case, dosing data was taken directly from MM-020 for Rd and MPT. Subsequent treatment costs are included using the distribution of subsequent treatments as seen in the MM-020 and VISTA trials. Health state costs were derived by estimating health care resources using a survey of seven clinicians. Unit costs for the resources were obtained from the 2015-16 National Reference Costs.

The results of the economic model are presented as incremental cost effectiveness ratios (ICERs), measured as the incremental cost per QALY. For the base case the incremental cost per QALY gained is £[redacted] for Rd compared to MPT and £[redacted] per QALY for Rd compared to VMP (Table 1 and Table 2). In the CS, the company acknowledges that Rd is not cost-effective compared to MPT and therefore they suggest the NICE appraisal committee consider the comparison between Rd and VMP for patients unable to tolerate or with contraindications to thalidomide.

Table 1 Base case results (with PAS) – vs MPT

Technologies	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER (per QALY)
MPT	£[redacted]	[redacted]	[redacted]				
Rd	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]

Table 2 Base case results (with PAS) – vs VMP in the subgroup of patients who are unable to tolerate or have contraindications to thalidomide

Technologies	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER (per QALY)
VMP	£[redacted]	[redacted]	[redacted]				
Rd	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]

In probabilistic sensitivity analyses, the probability of Rd being cost-effective compared to VMP is [redacted] and [redacted] at a willingness to pay threshold of £20,000 and £30,000 per QALY respectively. The company conducted deterministic sensitivity analyses on model parameters. The model results for Rd compared to VMP were most sensitive to changes in the hazard ratio for OS for VMP vs. MPT. The company conducted a range of scenario analyses to assess structural and methodological uncertainties. In none of these analyses did the ICER increase beyond £[redacted] per QALY.

Commentary on the robustness of submitted evidence

Strengths

- The literature searches conducted by the company were considered by the ERG to be appropriate and sufficiently comprehensive to have identified all the relevant clinical effectiveness evidence. The company's systematic review methods were also considered appropriate.
- The clinical effectiveness evidence for lenalidomide is based on a large international multi-centre RCT, the MM-020 trial (n=1623 patients randomised). The trial included a range of relevant outcome measures, including survival (e.g. OS, PFS), tumour response, HRQoL (including the EQ-5D as well as the cancer-specific instruments) and adverse events. The trial results can be considered mature with a median follow-up of 67 months at the most recent data cut-off (January 2016).
- The trial was judged by the company and the ERG to be of good methodological quality. However, it was open-label which raises the possibility of bias for some outcomes, such as self-reported HRQoL. The statistical procedures used in the MM-020 trial are clearly

reported in the CS and appropriate for evaluation of a cancer treatment. The randomised sample size and number of events achieved was adequate for the trial power calculations; an adequately defined ITT population was used for efficacy analyses. However, it is unclear how missing response data for HRQoL outcomes were handled.

- The company's economic model structure adequately represents the clinical pathway for patients with multiple myeloma.
- The methods used for the economic evaluations are consistent with the NICE reference case and methodological guidelines.
- A wide range of sensitivity analyses including one way, probabilistic and scenario analyses were conducted to assess the structural and methodological uncertainties of the economic model.

Weaknesses and areas of uncertainty

- The NMA which facilitates the indirect comparison of lenalidomide with bortezomib was conducted using standard methods. However, due to the limited available evidence the network containing four RCTs is sparse and most of the comparisons are informed by a single study. The comparator RCTs are of good methodological quality and have been included in previous NICE appraisals, though for some risk of bias domains the ERG's judgement was unclear, due to limitations in study reporting.
- Of the two statistical methods used to conduct the NMA (constant hazard ratios and fractional polynomials), the results of the fractional polynomial model varied according to which 'order' of model was chosen. There was wide uncertainty around the HRs for VMP in some of the fractional polynomial models, including the best fitting second-order model selected by the company. The constant hazard ratio statistical NMA appears to be the most appropriate model to inform the assessment as the results are associated with less uncertainty and the assumption of proportional hazards has been statistically confirmed.
- The CS suggests that the place of lenalidomide in the care pathway for first line treatment is as an alternative to bortezomib in patients unable to tolerate or contraindicated to thalidomide. The results of the economic evaluation show that lenalidomide can be considered cost-effective compared to bortezomib, but not compared to thalidomide. However, the MM-020 trial only compared lenalidomide with thalidomide. This raises the question of whether the results of this trial are generalisable

to patients intolerant or contraindicated to thalidomide. However, expert clinical advice to the ERG suggests that these results would unlikely to be different in such patients.

- There is a considerable amount of uncertainty associated with the prediction of the OS HR for VMP, which is estimated from the NMA.
- There is uncertainty about the assumptions made about subsequent treatments after first disease progression, pertaining to the comparison of Rd and VMP. VMP is only recommended by NICE in patients who are intolerant or contraindicated to thalidomide, yet in the company's base case analysis these patients can be treated with thalidomide as a subsequent treatment.

Summary of additional work undertaken by the ERG

The ERG conducted a series of additional analyses to address the issues surrounding time to treatment failure, treatment effectiveness of VMP vs MPT, HRQoL estimation, and subsequent treatment- and administration costs for VMP.

Our base case contains the following elements: changes to assumption relating to time to treatment failure, HRQoL estimation, subsequent line treatments and VMP administration costs. There are two versions of the base case model as shown below:

- Version 1: Includes ERG assumptions relating to time to treatment failure, HRQoL estimation and VMP administration costs.
- Version 2 (exploratory): In addition to the assumptions outlined in Version 1, this version includes ERG assumptions relating to subsequent treatments. Patients do not receive thalidomide as a subsequent treatment and those receiving Rd initially would not receive Rd as a subsequent treatment. This is considered exploratory as although it is informed by clinical practice considerations it differs from the subsequent treatments given in the MM-020 trial.

The results of the ERG base case are shown in Table 3 and Table 4. The ERG base case ICER for Rd compared to VMP in version 1 is £[redacted] per QALY gained which is an increase of £[redacted] from the company's base case ICER of £[redacted] per QALY. For the ERG base case exploratory version 2, the ICER is £[redacted] per QALY which is a decrease of £[redacted] from the company's base case ICER.

Table 3 ERG base case analysis results for Rd vs VMP (version 1)

Intervention / comparator	Costs	QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
VMP	£[redacted]	[redacted]			
Rd	£[redacted]	[redacted]	£[redacted]	[redacted]	£ [redacted]

Table 4 ERG base case analysis results for Rd vs VMP (version 2)

Intervention / comparator	Costs	QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
VMP	£[redacted]	[redacted]			
Rd	£[redacted]	[redacted]	£[redacted]	[redacted]	£[redacted]

The ERG's preferred base case analysis increases the ICER from the company's base case analysis, but it remains within the willingness-to-pay threshold of £30,000 per QALY.

1 Introduction to ERG Report

This report is a critique of the company's submission (CS) to NICE from Celgene on the clinical effectiveness and cost effectiveness of lenalidomide in combination with dexamethasone for previously untreated multiple myeloma. It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on 13/11/17. A response from the company via NICE was received by the ERG on 27/11/17 and this can be seen in the NICE committee papers for this appraisal.

References to the CS in this report refer specifically to Document B, the main company evidence submission document. Appendices, where cited, are referred to by the relevant appendix letter.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The ERG considers that the CS submission provides a clear and accurate overview of the condition. Multiple myeloma is a rare, incurable form of haematological cancer that arises from the monoclonal expansion of plasma cells in the bone marrow. These myeloma cells suppress the development of white and red blood cells that are responsible for fighting infection and carrying oxygen around the body, as well as platelets required for blood clotting. Multiple myeloma is primarily a disease of the elderly and at diagnosis, more than two-thirds of patients are aged ≥ 65 years[1] and nearly half are aged ≥ 75 years.[2]

Patients suffer from a range of debilitating symptoms, including skeletal destruction, leading to lytic bone lesions, pathological fractures, bone pain, mobility problems and osteoporosis. They also suffer impaired bone marrow function, recurrent infections, hypercalcaemia, anaemia and general ill health.[3] Myeloma cells secrete large quantities of an abnormal antibody (Ig paraproteins, termed M protein) which can result in renal insufficiency and kidney failure.[3 4] The CS states that the course of disease is not uniform and varies according to factors such as age, frailty, renal function, tumour load and genetic factors. Multiple myeloma is characterised by

cycles of remission followed by relapse and therefore requires continuous treatment to control the disease and prolong remission.

2.2 Critique of company's overview of current service provision

The CS provides a clear and accurate overview of the current service provision in England for the treatment of newly diagnosed multiple myeloma for both transplant eligible and transplant ineligible patients, according to the NICE clinical guidelines (CS section B.1.3; see Table 5 below).

Table 5 Current clinical pathway of care for patients with multiple myeloma in England (from CS Table 3)

Therapy line	Guidance	Transplant eligible patients with MM	Transplant ineligible patients with MM
1st Line	NICE TA311[5] NICE TA228[6]	• BOR + DEX or BOR + THAL + DEX induction followed by ASCT[5]	• THAL+ alkylating agent + corticosteroid (e.g. MPT) • If THAL intolerant /contraindicated BOR + MP[6] ○ **Proposed use of Rd**
2nd Line	NICE TA129[7] NICE TA457[8]	• BOR ± DEX having received 1 prior therapy[7] • CAR + DEX having received 1 prior therapy which did not include BOR • LEN + DEX (subject to ongoing NICE appraisal) • Conventional chemotherapy (including cyclophosphamide and melphalan) ± steroid[a] • A minority of patients may receive a second ASCT	
3rd Line onwards	NICE TA171[9] NICE TA380[10]	• LEN + DEX[9] • PANO + BOR + DEX[b 10]	
4th Line onwards	NICE TA427[11] CDF 2017[12]	• POM + LoDEX[11] • Daratumumab monotherapy (subject to ongoing NICE appraisal) • BEN combinations[d] (via CDF) where all other treatments contraindicated or inappropriate[12] • Conventional chemotherapy (inc. cyclophosphamide and melphalan) ± steroid ± THAL re-treatment[c]	

[a] Primarily received by patients who cannot tolerate THAL, have received BOR at first-line and have recently initiated 2nd line treatment as BOR retreatment is no longer funded by the CDF therefore availability is limited.
[b] PANO+BOR+DEX is reimbursed in patients who have received ≥ 2 prior lines of treatment including BOR + IMiD;
[c] THAL retreatment can only be used in patients who are THAL eligible (i.e., not those who are THAL intolerant or contraindicated); [d] BEN is usually used at 4th line onwards (via the CDF).
ASCT= autologous stem cell transplant; BEN = bendamustine; BOR =bortezomib; CAR = carfilzomib; CDF = Cancer Drugs Fund; DEX = dexamethasone; LEN = lenalidomide; LoDEX = low dose dexamethasone; MP = melphalan, prednisone; MPT = melphalan, prednisone, thalidomide; PANO =panobinostat; POM = pomalidomide; Rd = lenalidomide and low-dose dexamethasone until disease progression; THAL= thalidomide.

The company propose that lenalidomide with dexamethasone would partially displace first line bortezomib combinations (with an alkylating agent and a corticosteroid) (Table 5). The population specified in the company's decision problem is patients with previously untreated newly diagnosed multiple myeloma who are ineligible for stem cell transplantation. The patient population matches that specified in the final scope issued by NICE.

Lenalidomide (REVLIMID®), taken orally on days 1 to 21 of a 28 day cycle was granted a European Medicines Agency (EMA) marketing authorisation on 19th Feb 2015, for use as first line therapy for newly diagnosed multiple myeloma patients who are ineligible for stem cell transplantation with exclusion criteria as described in the CS table 6.[13] The Summary of Product characteristics (SmPc), states that the recommended starting dose of lenalidomide is 25 mg orally, once daily on days 1 to 21 of repeated 28-day cycles.[15] Lenalidomide is taken with a recommended dose of dexamethasone of 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance.

2.3 Critique of company's definition of decision problem

The comparator described in the NICE scope is thalidomide in combination with an alkylating agent and a corticosteroid. The company chose the combination of melphalan, prednisone and thalidomide (MPT). An alternative thalidomide combination is attenuated cyclophosphamide, thalidomide and dexamethasone (CTDa). Expert clinical expert advice to the ERG is that CTDa is widely used as a first line treatment in the UK. However, the company stated that CTDa is not considered a relevant thalidomide-based combination as it is unlicensed in the UK. They therefore used MPT as a suitable proxy. The CS states that MPT was considered by clinical specialists who took part in NICE TA228[6] to be equivalent in terms of toxicity and similar in terms of cost to CTDa. A meta-analysis published as a conference abstract identified by the ERG which indirectly compared MPT with CTD reported no difference between the two in PFS and OS.[16] For patients unable to tolerate or who have contraindications to thalidomide, the comparator in the scope is bortezomib in combination with an alkylating agent and a corticosteroid. The company included the combination of bortezomib, melphalan and prednisone (VMP) in the CS. Expert clinical expert advice to the ERG also highlighted that an additional first line treatment that is used in the UK is cyclophosphamide, bortezomib and dexamethasone (CVD). However, the ERG notes that although this combination has been used for first and second line treatment in the UK, it is unlicensed for first line use. Scoping searches

conducted by the ERG did not identify relevant trial evidence for its use in first line treatment that would allow it to be compared to lenalidomide.

The outcomes stated in the decision problem match with those defined in the NICE scope.

The NICE scope does not mention any patient subgroups to be assessed. The ERG is not aware of any other relevant subgroups that should have been included. The CS considers patients who are unable to tolerate, or have contraindications to thalidomide to be a subgroup in this appraisal stating "The final scope also identifies a subgroup of patients who are unable to tolerate, or have contraindications to thalidomide. The comparator for this subgroup is VMP" (CS, p 94). The ERG notes that the scope does not explicitly refer to this as being a patient subgroup, rather, it notes that bortezomib is the comparator treatment for people who are unable to tolerate, or have contraindications to thalidomide. Expert advice to the ERG estimates that around 50% of patients may be intolerant or contraindicated to thalidomide and factors influencing the choice of treatment vary. Whilst adverse effects of thalidomide can be difficult to tolerate some patients prefer thalidomide as it is an oral therapy in comparison to bortezomib which is administered either intravenously or subcutaneously.

The ERG does not consider there are any issues relating to equity or equality.

3 CLINICAL EFFECTIVENESS

3.1 Critique of company's approach to systematic review

3.1.1 Description of company's search strategy

The CS reports three systematic searches, all last updated in August 2017:

- Clinical-effectiveness (CS Appendix O)
- Cost-effectiveness (CS Appendix G)
- HRQoL (CS Appendix H)

All three searches were thorough and well documented for transparency. The databases selected (Medline, Embase, Cochrane Central Register of Controlled Trials) were relevant, the strategies contained a good range of descriptive subject headings, free text terms, acronyms for drug administration regimens and application of appropriate search filters. The search syntax was appropriate and the sets of search terms were correctly combined. It is uncertain why vincristine appeared as a term in all three searches. Vincristine does not appear in the inclusion

criteria for the systematic review, however the CS states that “eligibility criteria for interventions and comparators were developed prior to the release of the draft scope and were broader than required for the decision problem” [Appendix D, p 9]. The inclusion of the term did not detract from obtaining relevant results. A range of relevant conferences were searched including: the European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), the American Society of Haematology (ASH), the European Haematology Association (EHA), the International Multiple Myeloma Workshop and the International Study for Pharmacoeconomics (ISPOR). Some hand-searching was undertaken. Further grey literature manual searching was carried out using the Canadian Agency for Drugs and Technologies (CADTH), the National Institute for Health and Care Excellence (NICE), National Health Service Economic Evaluation Database (NHS EED), International Network for Agencies for Health Technology Assessment (INAHTA) and the National Institute for Health Research (NIHR). Clinicaltrials.gov was also searched for identification of ongoing studies and the company specifies in Section B.2.11 of the CS that in respect of “ongoing studies in transplant-ineligible patients with newly diagnosed multiple myeloma, there are no ongoing company-sponsored studies from which new evidence will become available in the timeline specified.”

The ERG searched Celgene’s website and the following clinical trial databases: UK Clinical Trials Gateway (UKCTG) and WHO International Clinical Trials Platform (WHO ICTRP). No additional RCTs or trials that matched the inclusion criteria were identified. Most results related to observational studies or to co-administration of drugs which were not specified in the scope or inclusion criteria. A separate adverse reaction search was not undertaken by the company as this information was extrapolated from the MM-020 trial. The ERG notes there was not a separate healthcare resource utilisation search nor were there specific free-text words to express resource use/utilisation in the cost effectiveness search, although health care costs were included as a descriptive subject heading.

In summary, the searches were well constructed, up to date and considered to be fit for purpose.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection

The company provides the inclusion criteria for their clinical effectiveness systematic review in CS Appendix D, Table 56.

The ERG's critique of the eligibility criteria used in the review for the NMA and details about the studies identified for inclusion are provided in section 3.2.

Population

The inclusion criteria for the population was limited to patients with newly diagnosed or untreated MM, who are unable to receive stem cell transplantation therapy and patients aged 65 years or over with newly diagnosed or untreated MM. Patients with relapsed or refractory multiple myeloma and trials with fewer than 10 patients per treatment arm were excluded.

Intervention

The systematic review included the following interventions: lenalidomide, thalidomide, bortezomib, melphalan plus prednisone, used either as monotherapy or as part of a combination therapy. Any treatment for newly diagnosed multiple myeloma, other than those stated were excluded. In what is described as a second phase, the inclusion criteria for the included studies were subsequently narrowed down to those relevant to the decision problem. The company states that the eligibility criteria for interventions and comparators were developed prior to release of the draft scope and were therefore broader than required for the decision problem. Subsequently, studies had to provide direct or indirect evidence on comparison between licensed doses of three combinations: Rd, MPT, and VMP.

Comparators

The included comparators were placebo, any of the interventions listed included interventions at a different dose or duration and any other active drug provided as monotherapy or as part of a combination therapy.

Outcomes

To be included, trials had to assess at least one of the following outcomes:

- Progression free survival (PFS)
- Overall survival (OS)
- Response
    - Complete response
    - Very good partial response
    - Partial response
    - Stable disease

- Progressive disease
- Adverse events

While the company's study eligibility criteria table (CS Appendix D, Table 56) does not include (TNT, TTF and HRQoL as outcomes as per the NICE final scope, these outcomes were included in the CS. TNT was reported in the form of AMT. The specified outcomes are therefore reflective of the NICE final scope. Overall, the ERG considers the outcomes listed in the company's decision problem are appropriate and clinically meaningful.

Design

The company's inclusion criteria were limited to RCTs published since 1/1/1988 and limited to those written using the English language. Studies with fewer than 10 patients were excluded. Setting was not used as an inclusion criterion nor any limits placed on inclusion relating to the quality of the RCTs, which is appropriate.

Subgroups

Subgroups were clearly stated as age, sex, geographical region and race; baseline International Staging System (ISS) disease stage and parameters of prognostic significance such as cytogenic profile, parameters of prognostic significance and biochemical profiles, Creatinine clearance, baseline albumin and lactate dehydrogenase (Section B.2.7.4). These characteristics are included as baseline data.

Equality issues

The CS states that no equality issues relating to the use of lenalidomide were identified or are anticipated.

Searches for the systematic review were conducted in three phases, an original search and two subsequent updates, detailed in CS Appendix D.1.1.2. The original search was carried out on March 14th 2016, followed by two further updates (8th Nov 2016 and 8th August 2017). The CS provides a PRISMA flowchart illustrating the number of records identified and included/excluded records at each stage of the SLR screening processes (CS Appendix D, Fig 25). Reasons for exclusion at the full paper stage are provided and references listed in Appendix D (CS Table 58).

Overall, the ERG notes that the systematic review inclusion criteria were broader than the decision problem and the NICE scope due to the reasons previously stated. Changes made by the company to the inclusion criteria of included studies during a 'second phase' of inclusion/exclusion screening however, rectified this.

3.1.3 Identified studies

The company's systematic review included four randomised controlled trials (RCTs), all of which were included in the network meta-analysis (NMA) (see section 3.1.7 of this report). Two of the studies compared MPT with MP (IFM-01/01 and IFM 99/06);[17 18] one compared VMP with MP (VISTA)[19-21] and one compared Rd with Rd18 and MPT (MM-020).[22 23] Only the latter trial met the inclusion criteria for the clinical effectiveness review and was used for marketing authorisation.

Some summary details of the MM-020 trial are presented in a table in the CS (CS Table 5), but the majority of details are presented in Appendix B. Only limited information (including trial design, patient numbers, study location and some baseline parameters) for the additional three trials included in the NMA (IFM 01/01; 99/01 and VISTA are provided[17-20] (Appendix D, Table 60 and 61).

To be included in the MM-020 trial, patients had to have newly diagnosed symptomatic multiple myeloma and had to meet the following three criteria for inclusion (Appendix B.2.3.2, Table 6):

- Monoclonal plasma cells in the bone marrow ≥ 10% and/or presence of a biopsy-proven plasmacytoma
- Monoclonal protein present in the serum and/or urine
- Myeloma-related organ dysfunction AND measurable disease by protein electrophoresis analyses in serum and/or urine.

Patients had to be age ≥18 years. Patients younger than 65 years of age had to be ineligible for stem cell therapy (SCT), decline SCT or were only included if SCT was not available. Patients also had to have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1 or 2.

The CS provides a CONSORT flowchart (CS Appendix D.1.2, Figure 32) detailing the number of patients that discontinued/dropped out (with reasons). The flowchart also includes the number

of patients still receiving treatment at the end of the trial (Rd arm only) or in PFS follow-up and the number of patients analysed in the ITT and safety population.

Summary details presented in table format were trial design (CS Appendix B.2.3.1, Figure 2), intervention and comparator dose and duration as well as population (see Table 7 below), outcomes (CS Appendix B.2.3.1, Table 10), methodological characteristics (CS Appendix B.2.3 Table 11) and statistical analyses including subgroups (CS Appendix B.2.4.3). Details of sample size calculations (CS Appendix B.2.4.1) and description of ITT analysis (CS Appendix B.2.4.3) were in separate sections rather than table format.

MM-020 was a three-arm RCT comparing the efficacy and safety of the two lenalidomide regimens, Rd and Rd18 with MPT. Treatment in the Rd arm consisted of lenalidomide and low-dose dexamethasone (oral dose of Rd for 21 days followed by 7 day's rest (21/28 day cycles) until disease progression or unacceptable toxicity. In the Rd18 arm, lenalidomide and low-dose dexamethasone were also given for a maximum of eighteen 21/ 28 day cycles (72 weeks). The MPT arm consisted of melphalan, prednisone and thalidomide given for maximum of twelve 42-day cycles (72 weeks). The company states that 60% of patients started thalidomide at dose of 200 mg and 40% of patients at dose of 100mg. Expert advice to the ERG is that in UK clinical practice, elderly patients would generally start on 50 mg and increase to 100 mg. Dose adjustments were made dependant on age, renal function, and neutrophil and platelet count, while dose delays and reductions were permitted in case of study treatment toxicity. Study drug dosing in each treatment arm can be seen in Table 6 below.

Table 6 MM-020 study drug, dose and duration

Study Arm	Drug and drug dosing
Rd	25 mg lenalidomide on days 1 to 21 of a 28-day cycle. 40 mg dexamethasone on days 1, 8, 15 and 22 of a 28-day cycle. Treatment until disease progression or unacceptable toxicity
Rd18	25 mg lenalidomide on days 1 to 21 of a 28-day cycle. 40 mg dexamethasone on days 1, 8, 15 and 22 of a 28-day cycle. Treatment for a maximum of 72 weeks (18 cycles)
MPT	0.25 mg/kg melphalan, on days 1 to 4 of a 42-day cycle. 2 mg/kg prednisone: on days 1 to 4 of a 42-day cycle. 200 mg thalidomide on days 1 to 42 of a 42-day cycle. Treatment for a maximum of 72 weeks (12 cycles)

Based on CS Table 7 in CS B.2.3.4.

Table 7 illustrates the baseline characteristics for the three arms of MM-020.

Table 7 Baseline characteristics of patients in MM-020

Characteristic	MM-020 (n = 1,623)		
	Rd (n = 535)	**Rd18 (n = 541)**	**MPT (n = 547)**
Median age (min–max), years	73.0 (44.0–91.0)	73.0 (40.0–89.0)	73.0 (51.0–92.0)
Age distribution,[a] n (%)			
≤ 75 years	349 (65.2)	348 (64.3)	359 (65.6)
> 75 years	186 (34.8)	193 (35.7)	188 (34.4)
Male, n (%)	294 (55.0)	273 (50.5)	287 (52.5)
Race, n (%)			
Asian	40 (7.5)	43 (7.9)	44 (8.0)
Black/African–American	9 (1.7)	6 (1.1)	5 (0.9)
Hawaiian/Pacific Islander	1 (0.2)	0 (0.0)	1 (0.2)
White/Caucasian	474 (88.6)	480 (88.7)	491 (89.8)
Other	6 (1.1)	11 (2.0)	3 (0.5)
Undisclosed	5 (0.9)	1 (0.2)	3 (0.5)
ECOG performance status, n (%)			
0	155 (29.0)	163 (30.1)	156 (28.5)
1	257 (48.0)	263 (48.6)	275 (50.3)
2	119 (22.2)	113 (20.9)	111 (20.3)
≥ 3	2 (0.4)	2 (0.4)	2 (0.4)
Missing	2 (0.4)	0 (0.0)	3 (0.5)
ISS staging,[b] n (%)			
Stage I or II	319 (59.6)	322 (59.5)	323 (59.0)
Stage III	216 (40.4)	219 (40.5)	224 (41.0)
Beta-2-microglobulin, n (%)			
> 5.5mg/L	224 (41.9)	224 (41.4)	234 (42.8)
≤ 5.5mg/L	309 (57.8)	316 (58.4)	312 (57.0)
Missing	2 (0.4)	1 (0.2)	1 (0.2)
Creatinine clearance, n (%)			
< 30 mL/min	45 (8.4)	47 (8.7)	55 (10.1)
≥ 30–50 mL/min	126 (23.6)	120 (22.2)	126 (23.0)
≥ 50–80 mL/min	241 (45.0)	252 (46.6)	222 (40.6)
≥ 80 mL/min	123 (23.0)	122 (22.6)	144 (26.3)
Cytogenetic risk,[c] n(%)			
Adverse risk	170 (31.8)	185 (34.2)	189 (34.6)
Non-adverse risk	298 (55.7)	290 (53.6)	283 (51.6)
Favourable hyperdiploidy	112 (20.9)	103 (19.0)	102 (18.6)
Normal	148 (27.7)	131 (24.2)	141 (25.8)

Uncertain risk	38 (7.1)	56 (10.4)	39 (7.1)
Non-evaluable	34 (6.4)	35 (6.5)	45 (8.2)
Missing	33 (6.2)	31 (5.7)	31 (5.7)
Multiple myeloma subtype			
IgA	138 (25.8)	142 (26.2)	123 (22.5)
IgA and IgG	7 (1.3)	6 (1.1)	8 (1.5)
IgA and IgM	0 (0.0)	0 (0.0)	1 (0.2)
IgD	4 (0.7)	7 (1.3)	4 (0.7)
IgG	334 (62.4)	331 (61.2)	350 (64.0)
IgM	3 (0.6)	1 (0.2)	1 (0.2)
Not available (includes light chain disease)	49 (9.2)	54 (10.0)	60 (11.0)

Table based on CS Table 12 in CS section B.2.3.7[23]

[a] Patients were stratified at randomisation by age (≤ 75 years vs > 75 years).

[b] Patients were stratified at randomisation by stage (stage I or II vs stage III).

[c] Cytogenetic risk categories are mutually exclusive.

Definitions: adverse risk categories: t(4;14), t(14;16), del(13q) or monosomy 13, del(17p), 1q gain; non-adverse risk categories: favourable hyperdiploidy (t[11;14], gains of 5/9/15, normal, a normal result, gains other than 5/9/15, IgH deletion, and uncertain risk. Probes used for analysis cannot place patient in any of the other risk categories. Not evaluable: no specimen received, test failure or insufficient number of cells available for analysis.

Generally, the ERG agrees with the CS that baseline characteristics between study arms for MM-020 were well balanced and there were no significant differences between age, gender, race or biochemical parameters between the intervention and comparator groups. There are some minor differences in creatinine clearance, cytogenetic risk and multiple myeloma subtype between treatment arms. Upon request from the ERG, the company provided details of the use of concomitant therapy during the active treatment phase in the safety population per treatment arm. The safety population was defined as all randomised patients who received at least one dose of the study treatment. Although the therapies provided during the active treatment phase were similar between the treatment arms, the ERG noted that a higher number of patients were given warfarin in the Rd arm (6% vs 2.8% Rd18 and 3.1% MPT) and administration of Granulocyte-colony stimulating factor (GCSF) was lower in both the Rd and Rd18 treatment arms compared to MPT (17.5% Rd; 17.2% Rd18; 34.8% MPT).

The ERG consider that all relevant RCTs have been identified in the systematic review and that included RCTs meet the company's inclusion criteria.

The company states that in transplant-ineligible patients with newly diagnosed multiple myeloma, there are no ongoing company-sponsored studies from which new evidence will

become available in the timeline of this appraisal. The ERG has not identified any further potential studies.

3.1.4 Description and critique of the approach to validity assessment

The company quality assessed the one lenalidomide trial included in the CS (referred to as MM-020 in the CS and FIRST in the journal publication[22]) using the NICE suggested criteria.[24]

The ERG independently assessed the methodological quality of the trial and compared judgements with those of the company (Table 8). There were no differences in judgements between the company and the ERG (though note that the company answered three questions without a direct yes/no judgement). There was an absence of judgement in the CS regarding the concealment of treatment, blinding and intention-to-treat (ITT) analysis (see section 3.1.6 of this report for further description and critique of the trial's statistical methods). Concealment of treatment and ITT analysis were judged to be adequate by the ERG, with partial blinding used in the trial (see Table 8), however, it is unclear how missing HRQoL data were handled.

Table 8 Company and ERG assessment of the MM-020 trial quality

NICE quality assessment criteria for RCT[24]	**Judgements**	**MM-020**[22 23]
1. Was the method used to generate random allocations adequate?	CS:	Yes
	ERG:	Yes
ERG comments: Patients were stratified at randomisation by age (≤ 75 years versus > 75 years), stage (ISS stages I or II versus stage III) and country.		
2. Was the concealment of treatment allocation adequate?	CS:	"Open-label"
	ERG:	Yes
ERG comments: The company does not provide a judgement for this question, but states that this is an open-label study. Allocation concealment is different to blinding and means that the person randomising the patient does not know what the next treatment allocation will be. The trial used interactive voice-response system to randomly assign patients in a 1:1:1 ratio and concealment of treatment allocation was therefore judged to be adequate by the ERG.		
3. Were the groups similar at the outset of the study in terms of prognostic factors?	CS:	Yes
	ERG:	Yes
ERG comments: Baseline characteristics across the treatment arms presented in the CS were generally well balanced, with some minor differences in creatinine clearance, cytogenetic risk and multiple myeloma subtype between treatment arms (CS Table 12). The CS did not report prior medication at baseline by treatment arm, but reported in the clinical study report (CSR) that the use of medication prior to the study was consistent with medical history, with no clinically notable differences observed across the 3 treatment arms.		

4. Were the care providers, participants and outcome assessors blind to treatment allocation?	CS:	"Open-label"
	ERG:	Partially
ERG comments: The company does not provide a judgement for this question, but states that this was an open-label RCT, with the independent response adjudication committee (IRAC) blinded to treatment allocation reviewing the efficacy data independent of investigator-reported response. In addition, the study team was blinded to the data until after the database lock (CS Appendix B, Table 11). However, it would appear that patients were not blinded to which treatment they received.		
5. Were there any unexpected imbalances in drop-outs between groups?	CS:	No
	ERG:	No
ERG comments: Study discontinuations (i.e. patients discontinuing treatment and patients no longer in PFS follow up phase) were generally balanced between the trial arms (86.5% Rd, 95.2% Rd18 and 95.6% MPT). The CS states that the majority of patients in the trial arms discontinued treatment due to progressive disease (50.7% Rd, 66.9% Rd18 and 61.6% MPT) and adverse events (12.0% Rd, 13.1% Rd18 and 13.9% MPT). Death was the reason for study discontinuation in 11.2% of patients in the Rd treatment arm, 5.2% in the Rd18 and 6.8% in the MPT treatment arm. The number of discontinuations due to loss to follow-up and protocol violations was very low (≤ 0.7%). In response to a clarification question (question A8), the company provided a breakdown of discontinuations list under 'other' [Rd n=50, Rd18 n=34 and MPT n=46 (CS Appendix D.1.2, Figure 32)]. The table lists the reasons for withdrawal individual patients, but does not provide an aggregate categorisation of them (response to clarification question A8, Table 3). The reasons included patient or family withdrawal, non-compliance and disease-related reasons (i.e. intolerance to therapy).		
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	CS:	No
	ERG:	No
ERG comments: None		
7. Did the analysis include an intention-to-treat (ITT) analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	CS:	ITT population and safety population, with appropriate censoring methods
	ERG:	Yes Yes
ERG comments: The company does not provide a judgement for this question, but states that analysis was by ITT population and safety population, with appropriate censoring methods. The CS states that missing assessments or discontinuations due to reasons other than progressive disease were handled by FDA guidelines[25] and that alternative censoring rules based on the EMA guideline[26] on the evaluation of anti-cancer medicinal products were used as a sensitivity analysis (Table 66 in Appendix D.1.3). Censoring methods appear to be appropriate. It should be noted that it is unclear how missing HRQoL data were handled.		

3.1.5 Description and critique of company's outcome selection

All of the outcome measures included in the CS match those in the NICE scope. There are no outcomes from the scope that are omitted from the CS. Data for all of the outcomes are available from the MM-020 trial, for the comparison of Rd with MPT. For the comparison of Rd

with VMP outcome data for OS and PFS are available from the NMA (see section 3.1.7 of this report).

CS Table 10 succinctly defines the outcomes included in the CS, the data cut-offs available from the MM-020 trial as well as which outcome data are used in the economic model. Additional details on how outcomes were defined in the trial are presented in CS Table 13.

Two data cut-offs are available for the MM-020 trial: 24th May 2013 and 21st January 2016. For all outcome data used in the economic model the latter data cut-off is used; this represents the longest follow-up available from the trial (with a median follow-up of 67 months).

3.1.5.1 Survival

PFS was the primary outcome in the MM-020 trial and was defined as time from randomisation until documented disease progression or death, whichever occurred earlier. This is consistent with standard definitions of PFS.[26] For PFS the 24th May 2013 was the pre-planned data cut-off with final analysis. Data are provided at this data cut-off based on Independent Response Adjudication Committee (IRAC) assessment using both FDA and EMA censoring criteria. The IRAC used the International Myeloma Working Group (IMWG) criteria for assessing progression.[27] PFS data for the 21st January 2016 data cut-off are also provided based on investigator assessment using FDA and EMA censoring criteria (N.B. the IRAC was disbanded in 2013 and therefore only an investigator assessment was available for the 2016 data cut-off). These data are described in the CS as post hoc updated analyses and are used to inform the economic model.

An additional exploratory (post hoc) PFS analysis was performed: progression-free survival 2 (PFS2). This was defined as the time from randomisation to second objective progressive disease, start of third-line therapy or death from any cause, whichever occurred first (CS Table 13). This outcome was included to assess response in patients who have progressed following first line treatment and received a subsequent line of treatment. Specifically, whether the PFS benefit observed with first line lenalidomide is maintained with the next line of therapy. The CS suggests that, theoretically, experimental treatments can increase long-term toxicity or alter the tumour population or microenvironment to induce drug resistance or evolution of an aggressive clone (CS Appendix L.1.1). Hence, there is a need to assess whether the first line treatment causes a negative response to subsequent treatment. The CS states that PFS2 has been acknowledged by the EMA as a suitable alternative endpoint for maintenance regimens. The

PFS2 data presented in the CS is for the 21st January 2016 data cut-off. PFS2 is not included in the company's economic model.

Data for OS from the 24th May 2013 data cut-off (a planned interim analysis) are reported in the trial journal publication, whilst data from the 21st January 2016 data cut-off (final planned analysis) are reported in the CS. The final OS analysis was planned for when all patients had been followed for five years or had died or been lost from follow-up before five years. OS data at the Jan 21st 2016 cut-off are used to inform the economic model.

3.1.5.2 Response rates

Tumour response rates are also available for the 24th May 2013 data cut-off in the journal publication and the 21st January 2016 data cut-off in the CS. The 2013 data cut-off was based on investigator and IRAC assessments (the latter using IMWG criteria and described as the primary response analysis), whilst the 2016 data cut-off was based on investigator assessment only (as stated above, the IRAC was disbanded in 2013). Tumour response is categorised in terms of CR, VGPR, PR, SD and PD. These categories are not defined in the CS, though they are defined in an appendix to the trial journal publication (Table s12)[22] and are based on the International Uniform Response Criteria for Multiple Myeloma.

The CS reports the overall response rates (ORR) for the 21st January 2016 data cut-off, defined as the number of confirmed responders (CR, VGPR and PR maintained for at least 6 weeks) divided by the number of patients in the intention to treat (ITT) population for the primary analysis of response rate (CS Table 13). The CS also reports DoR for the 21st January 2016 data cut-off, which is defined as the time when the response criteria were first met for CR, VGPR, or PR until the first date the response criteria were met for progressive disease, or until the subject died from any cause, whichever occurred first (CS Table 13). Time to response (TTR) is reported in the CS as the time from randomisation to the time the response criteria for CR, VGPR, or PR were first met (CS Table 13).

The CS also makes brief reference to a "deeper quality" response as including patients with CR or VGPR (CS section B.2.6.6)

Response rates, whilst an important measure of clinical effectiveness, are not used as an input parameter to inform the company's economic model. This is appropriate as survival rates are the key clinical effectiveness parameters informing the model.

3.1.5.3 Other outcomes

Time to treatment failure (TTF) is defined as the time from randomisation to discontinuation of study treatment for any reason (e.g. disease progression, toxicity, start of another anti-myeloma treatment and death). Data are presented for both the 24th May 2013 data cut-off in the trial journal publication (supplementary appendix) and for the 21st January 2016 data cut-off in the CS (IRAC and investigator assessment, respectively). TTF is used as an input parameter in the economic model to calculate the proportion of patients on treatment in each model cycle.

Time to next treatment/second-line anti-myeloma treatment is defined as the time from randomisation to the start of a non-protocol anti-myeloma treatment. Data are presented for the 24th May 2013 data cut-off in the trial journal publication (supplementary appendix) and for the 21st Jan 2016 data cut-off in the CS (investigator assessment only). These data are not included in the economic model.

Adverse events are reported for the 24th May 2013 data cut-off in the trial journal publication (supplementary appendix) and for the 21st Jan 2016 data cut-off in the CS (investigator assessment only).

HRQoL was assessed in the MM-020 trial using three instruments: the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30), the EORTC Quality of Life Questionnaire–Multiple Myeloma 20 (QLQ-MY20), and the EuroQol 5-dimension European Quality of Life questionnaire (EQ-5D). The EORTC QLQ-C30 is a standard instrument for assessing HRQoL in cancer studies, and contains 30 items. Disease specific adaptations have been made for a number of cancers, including multiple myeloma. The QLQ-MY20 contains 20 questions specific to myeloma, including questions about bone, back and chest pain, and burning sensations in the eyes. The company report that this instrument has been subjected to validation in a peer-reviewed publication[28] (clarification question A5). The EQ-5D is a standard five dimension generic quality of life instrument which can generate utility data. These three instruments were administered to patients at baseline, at the end of selected study cycles and at study discontinuation (a maximum of 18 cycles (months) to permit a comparison between Rd and MPT – data cut-off 24th May 2013).

The CS reports that the main HRQoL analysis focused on six pre-selected and clinically relevant HRQoL domains: two from the QLQ-MY20 (Disease Symptoms and Side Effects of

Treatment) and four from the QLQ-C30 (Global Health Status, Physical Functioning, Fatigue, and Pain) in addition to the EQ-5D utility value. These domains, chosen before data analysis were informed by a workshop discussion with haematologists and based on perceived clinical relevance.

EQ-5D data from this trial are used in the economic model for Rd and MPT. CS Table 10 indicates that data from the 24th May 2013 data cut-off are available, but not the 21st January 2016 data cut-off, though in contradiction, the table indicates that the latter is used in the economic model. HRQoL data for VMP are based on QLQ-C30 data from the VISTA trial[29] which were mapped to EQ-5D using a published algorithm (this is discussed further in section 4.3.6 of this report).

In summary, the CS includes all of the outcomes in the NICE scope, with the MM-020 trial providing data for all outcomes. All outcome data for this trial are from the most recent data cut-off on the 21st January 2016. The assessment of the outcomes, in terms of definitions, appears to be standard for cancer trials.

3.1.6 Description and critique of the company's approach to trial statistics

3.1.6.1 Sample size

The primary outcome in the MM-020 trial was PFS for the comparison of Rd with MPT. A statistical power calculation is reported in the CS (section B.2.4.1). For a 24 month accrual period and a 36 month follow up period, a sample size of 530 patients in each treatment arm would have 80% power to detect a HR of 1.25 using a two sided log-rank test with an overall statistical significance level of 0.05. This calculation was based on assumptions including a clinically relevant improvement in median PFS of 25% and an exponential overall PFS distribution. The ERG noted a discrepancy between the CS and the trial journal publication,[22] with the latter stating that the HR in the power calculation was 0.80 rather than 1.25. The ERG asked the company to clarify this discrepancy (clarification question A3). The company acknowledged the lack of clarity and reported that the HR in the CS was presented with reference to the MPT arm hazard: 0.80, whilst the HR in the journal publication was presented with reference to the Rd-arm hazard: 1.25. The ERG notes that the required sample size was achieved as a total of 1623 patients were randomly assigned to treatment groups (Rd n=535; Rd18 n=541; MPT n=547).

The secondary analysis was between Rd, Rd18 and MPT with 950 patients were required to have disease progression or to have died across all treatment arms (log-rank test with 80% power).

For the comparison of final OS, a total of 597 deaths were expected in the Rd and MPT arms within five years (896 deaths across all three treatment arms). Based on a 25% improvement in median OS and 597 deaths, a two-sided log-rank test with significance level of 0.05 would give a power of 78%. The ERG notes that there were a total of 623 deaths across the Rd and MPT arms and 906 deaths across the three arms, therefore the number or events and thus the overall sample size was adequate.

3.1.6.2 Analysis populations

The CS defines three patient analysis populations: the ITT population, the efficacy-evaluable population and the safety population (CS Section B.2.4.2).

The ITT population comprised all randomised patients irrespective of whether they received study treatment, analysed according to the treatment to which they were randomised rather than treatment they actually received. This is the standard definition of ITT in clinical trials. The CS states that all efficacy endpoint analyses were based on the ITT population. The ERG has checked the results presented in the CS and agrees that ITT analysis was used based on the information reported. However, it is not stated how missing response data or missing HRQoL data were estimated. In the case of the latter, the ERG notes that the denominators reported in a journal publication by Delforge et al.[29] are never as high as the total number of randomised patients, around 88% - 92% at treatment cycle 1 and denominators decline over subsequent cycles (78 - 84%). This raises an uncertainty in the interpretation of the HRQoL results.

In the case of the latter, the ERG notes that the denominators (i.e. those patients available to be assessed) reported in a journal publication by Delforge et al.[29] are never as high as the total number of randomised patients, around 88%-92% at treatment cycle one and declining over subsequent cycles (52%-55% at month 18). The compliance rates at each cycle (that is, the percentage of patients responding as a proportion of the patients available) ranged from 86% to 92% at cycle one. Compliance rates were similar between Rd and MPT, except at month 18 when there was a lower rate in the MPT group (in the range 15% to 20%). This raises an uncertainty in the interpretation of the HRQoL results as it is not known how missing data were imputed in the ITT analysis.

HRQoL data for the two Rd arms were combined into one overall group post-hoc for presentation of results. This was done because the regimens were identical over the 18 month measurement period. The ERG requested the HRQoL results for the two Rd treatment arms separately, for transparency and these were subsequently provided by the company (clarification question A4). The ERG notes that the results for the two Rd treatment arms, as supplied by the company on request, [redacted]. Furthermore, the patient baseline characteristics were similar between the Rd and Rd18 groups, and the treatment given was identical over the 18 month period that HRQoL was measured. The decision to pool the two arms is therefore reasonable in this instance.

The CS states that cross-over to different treatment arms were not permitted, though patients did receive subsequent lines of treatment after disease progression. The OS estimates from the MM-020 trial are likely to be influenced by the effects of subsequent anti-myeloma treatment lines (the planned primary analysis of OS was after all patients had been followed for five years or had died or been lost from follow-up before five years). Around 56% of patients of the Rd group and around 70% of both the Rd18 and MPT groups received subsequent treatment with the same or an alternative anti-myeloma drug upon initial disease progression. The CS does not discuss the likely impact of this on the trial results. The ERG notes that second and third line treatment in the Rd arm mainly comprised bortezomib-based therapy (CS Table 46). Second and third line treatment in the MPT arm comprised mainly bortezomib or Rd. The OS results of this trial may not necessarily be generalizable to settings in which different subsequent line treatments are given. For tumour response, responses documented after patients received any other anti-myeloma treatment were not counted as responses. Thus, the tumour response data presented only reflect the initial treatment given (i.e. Rd or MPT).

The efficacy-evaluable population comprises ITT patients who met protocol requirements and were evaluated after receiving at least one dose of study treatment. The CS does not provide any further details of this population and whether any results for this population are reported in the CS or used in the economic model. The company clarified that the efficacy-evaluable population was a secondary population for the efficacy analyses which was not used (response to clarification question A6).

The safety population comprised ITT patients who met protocol requirements and were evaluated after receiving at least one dose of study treatment (lenalidomide, dexamethasone, melphalan, prednisone or thalidomide). Patients were analysed according to the initial treatment received. The number of patients included in the safety population was 1613 (out of 1623 randomised). This population was used in the analysis of adverse events, deaths and laboratory test results.

3.1.6.3 Censoring

Censoring was performed for PFS to account for patients who either discontinued the study or who did not have the event of interest during the study assessment period, or who began a new anti-myeloma regimen prior to progression. For the primary analysis of PFS the 2007 FDA censoring rules were used (CS Appendix C.1.2.1). In addition, 2012 EMA censoring guidance was used for PFS in a sensitivity analysis, thus allowing a comparison with censoring based on the FDA rules. Both of these censoring methods were used for the 24th May 2013 data cut-off (primary analysis of PFS) and the 21st January 2016 (post hoc) data cut-off. This latter data cut, used in the economic model is based on EMA censoring only. The CS states that the PFS results were similar between both censoring methods and the ERG agrees that this is the case, noting that the EMA censored results are slightly more conservative (slightly higher HRs as reported in CS Table 14).

3.1.6.4 Statistical procedures used

The CS reports that a hierarchical group sequential-testing procedure with appropriate alpha-spending functions, multiple-arm comparison and multiplicity adjustment was used to control the family-wise type-1 error rate in the interim and final analyses of endpoints (CS section B.2.4.3). Both OS and PFS were compared between treatment arms using an unstratified log-rank test with a two-sided significance level of 0.05. The Kaplan-Meier method was used to estimate survival distributions for each treatment arm, for both PFS and OS.

Procedures for analysing other time to event outcomes (i.e. DoR; TTP; TTF; PFS2) were reported to be the same as used for analysing PFS. The exception was the TTR outcome which is stated to have been compared between treatment arms using the Wilcoxon rank sum test, with subjects with the longest time to response having the highest rank. The statistical procedures used to assess the other outcomes (e.g. HRQoL; response) are described in CS Table 13.

3.1.6.5 Sub-groups

Subgroup analyses from the MM-020 trial are reported (CS Section B.2.7, and CS Appendix E). Pre-planned sub-group analyses comparing Rd with MPT were conducted for PFS, PFS2, OS and myeloma response outcomes. However, the CS only reports the results of these analyses for PFS and OS (at the 21st January 2016 data cut-off and for the ITT population). The subgroups presented in the CS include the trial's randomisation stratification factors (age, baseline International Staging System (ISS) disease stage, geographical region) and a number of other variables such as sex and race and parameters of prognostic significance. One of these parameters was stated to be baseline cytogenetic categories (high risk versus non-high risk: non-high risk includes patients with favourable hyperdiploidy, normal, and uncertain risk cytogenetic risk profiles). Clinical advice to the ERG is that cytogenetics are one of the key prognostic factors in multiple myeloma. It does not appear that any clinically relevant subgroups were not included.

The statistical procedures for conducting the sub-group analyses were the same as used for the main analysis of primary and secondary outcomes. Caution is required in the interpretation of the results as for some sub-groups the number of patients was relatively small and is therefore likely to be underpowered.

For both PFS and OS the CS states that exploratory analysis, based on a Cox proportional hazards regression model, were conducted in order to assess the demographic and prognostic factors that most affected treatment outcome (CS Table 13). The trial protocol (an appendix to the trial journal publication) states that this was done so that the treatment comparisons could be adjusted for these factors.

The CS also reports post-hoc sub-group analyses based on depth of response, for PFS and OS. This is defined as a best overall response of ≥ VGPR based on investigator assessment (CS section B.2.7.4.1). This appears to refer to the deeper quality of response to therapy mentioned on CS page 54, comprising patients with either a CR or a VGPR to treatment.

3.1.6.6 Summary

In summary, the statistical procedures used in the MM-020 trial are clearly reported in the CS and appropriate for evaluation of a cancer treatment. The randomised sample size and number of events achieved was adequate for the trial power calculations; an adequately defined ITT population was used for efficacy analyses and both EMA and FDA censoring rules were

employed for survival analyses. However, it is unclear how missing response data for HRQoL outcomes were handled.

3.1.7 Description and critique of the company's approach to the evidence synthesis

The CS provides a narrative review of the results of the MM-020 trial. Given that this was the only lenalidomide study included in the company's systematic review, it was not possible to do a meta-analysis. However, a network meta-analysis (NMA) was conducted to compare lenalidomide with bortezomib indirectly as no direct comparison of these treatments was identified in the systematic review.

The process for searching and screening studies for inclusion in the NMA was the same one used to identify studies of the clinical effectiveness of lenalidomide (as described earlier 3.1.1).

The ERG conducted a quality assessment of the NMA (Table 9).The following sections describe and critique the NMA in more detail.

Table 9 ERG quality assessment of NMA

Criterion	ERG assessment
NMA purpose	
1. Are the NMA results used to support the evidence for the clinical effectiveness of the intervention?	**Yes**, for the indirect comparison between Rd and VMP. The comparison of Rd and MPT is informed by the MM-020 trial (which is included in the NMA).
2. Are the NMA results used to support the evidence for the cost-effectiveness of the intervention?	**Yes**. The NMA results are used to indirectly compare Rd with VMP in the economic model since there was no direct evidence comparing these two treatments.
Evidence selection	
3. Are inclusion/exclusion criteria adequately reported?	**Yes**. In CS Appendix D.1.1.2 a list of excluded studies and full text review with reason for exclusion is provided.
4. Is quality of the included studies assessed?	**Yes**, section D.1.3 provides a Cochrane risk of bias assessment for each of the four included RCTs. The ERG did an independent risk of bias assessment of these trials to compare judgements with the company (appendix to this report).
Methods – statistical model	
5. Is the statistical model described?	**Yes**. Briefly in CS section B.2.9 and in more detail in CS Appendix D.1.1.5. Two types of statistical model are provided: one with constant HRs assuming proportional hazards (described as the primary analysis) and one using time-varying HRs informed by fractional polynomials (used as a scenario in the cost effectiveness analysis).

6. Has the choice of outcome measure used in the analysis been justified?	**Yes**. The NMA includes OS and PFS only. These outcomes directly inform the economic model.
7. Has a structure of the network been provided?	**Yes.** CS Figure 14 (Figure 1 in this report) provides a visual illustration of the network.
8. Is homogeneity considered?	**Yes**. CS Appendix D.1.1.4 discusses the comparability of the trials in terms of potential effect modifiers.
9. Are the studies homogenous in terms of patient characteristics and study design?	**Yes.** The company commented that baseline characteristics were well distributed across the four included trials. There is no statistical test of homogeneity for each of the pairwise comparisons in the NMA, however, this is appropriate as there was only one comparison that was informed by more than a single trial (MPT vs MP, n=2 trials).
10. If the homogeneity assumption is not satisfied, is clinical or methodological homogeneity across trials in each set involved in the indirect comparison investigated by an adequate method? (e.g. sub group analysis, sensitivity analysis, meta-regression)	**Not applicable**, see above.
11. Is the assumption of similarity stated?	**Yes,** in terms of a discussion about the comparability of the trials (see CS Appendix D.1.1.4). The CS notes that there was an approximate 10% difference in baseline ISS stage between one of the MP vs MPT trials and the MM-020 trial. The company suggested that this degree of variation is unlikely to violate the transitivity assumption for the NMA. Expert clinical advice to the ERG is that a 10% difference in ISS stage would not be important.
12. Is any of the programming code used in the statistical programme provided (for potential verification)?	**No**.
Sensitivity analysis	
13. Does the study report sensitivity analyses?	**No**. However, the company did supply alternative fractional polynomial model-based NMA analyses at the request of the ERG (clarification question A15).
Results	
14. Are the results of the NMA presented?	**Yes.** In CS section B.2.9 and in response to ERG clarification question A15 for additional fractional polynomial models.
15. Does the study describe an assessment of the model fit?	**Yes**. The deviance information criterion (DIC) was used to compare the goodness-of-fit of the competing fractional polynomial survival models.
16. Has there been any discussion around the model uncertainty?	**No.**
17. Are the point estimates of the relative treatment effects	**Yes**. HRs are provided accompanied by credible intervals (CS Table 18 and Table 20). For the time-

accompanied by some measure of variance such as confidence intervals?	varying HRs generated by the fractional polynomial model, a graphical illustration is given of the HRs curves for each treatment over time accompanied by curves representing the associated credible intervals (CS Figures 15 and 16).
Discussion - overall results	
18. Does the study discuss both conceptual and statistical heterogeneity?	**Yes**. The NMA was conducted using a fixed effect model. The CS states that a random effects model was not used because the network was sparse (only one trial informed each connected node in the network except for the MPT to MP connection) (CS Appendix D.1.1.5).
Discussion - validity	
19. Are the results from the indirect/NMA compared, where possible, to those just using direct evidence?	**No.** This was not necessary as there are no comparisons informed by both direct and indirect evidence.

3.1.7.1 Evidence network

Four RCTs were included in the network, as identified from the systematic review. Only one trial each for lenalidomide and bortezomib were included, whilst two trials of MP (versus MPT) were included.[17-21 30-32]

Figure 1 reproduces the network from CS Figure 14. It is a simple network which uses MP and MPT to connect Rd to VMP. The network contains direct comparisons (Rd versus MPT, MPT versus MP, VMP versus MP) and indirect comparisons (VMP versus MPT, VMP versus Rd). However, there are no comparisons informed by both direct and indirect evidence (i.e. a 'closed loop').

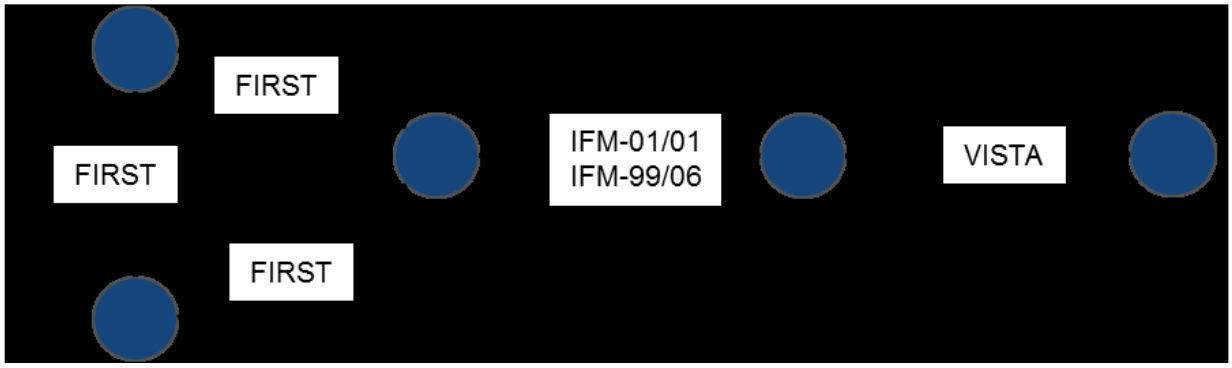


Figure 1 Network of trials in the NMA (from CS Figure 14)

The company excluded the trial by Sacchi et al.[33] from the systematic review because patients received between 6 and 12 cycles of MP instead of the licensed 12 cycles (CS Appendix D 1.1.2). The ERG notes that the results of this study were consistent to the other two studies comparing MP with MPT in the NMA (PFS HR of 0.5 (95% CI 0.3-0.9)[33] compared with a HR of 0.56 (95% CrI 0.46 - 0.68) from the NMA). Omission of this study is therefore unlikely to change the overall results of the NMA. The ERG also notes that there are other studies comparing MP with MPT excluded from the CS,[34-37] (CS Appendix D, Table 59) for the reason "does not provide direct or indirect evidence for comparison between Rd, MPT or VMP". These trials appear to have varying treatment durations to the licensed 12 cycles, however, the CS does not explicitly report whether this was the reason for exclusion. The ERG considers that all relevant evidence should be included in the NMA, however, the variations in the dosages used may compromise assumptions of similarity between the included trials, and increase uncertainty in the findings. This could have been explored via sensitivity analysis.

3.1.7.2 Risk of bias in trials included in the NMA

The CS provides a Cochrane risk of bias criteria assessment[38] of the four RCTs included in the NMA (CS Appendix D.1.3). The ERG conducted an independent risk of bias assessment of the trials and compared judgements with those of the company (see Appendix to this report). Of note, the three comparator studies included in the NMA (that is, of MP vs MPT and VMP vs MP) were included in a previous multiple technology appraisal of bortezomib and thalidomide for first line treatment of multiple myeloma (NICE TA228).[6] We therefore referred back to our previous critical appraisal of these trials for this current appraisal to ensure consistency.

The company judged the trials to be at low risk of selection bias (due to adequate randomisation), detection bias and other sources of bias. However, the CS states that concealment of random allocation to study groups was poorly described, potentially leading to selection bias. Most trials were judged unclear or high risk for performance bias due to lack of blinding of participants. The CS judges the trials to be at low risk for detection bias, as the outcomes were not likely to be influenced by lack of blinding.

The ERG's assessment of these trials mostly agrees with those of the company. However, contrary to the company, the ERG considered that due to the open-label nature of the studies, the risk for detection bias was high for the MM-020 and VISTA trials. The ERG were unable to assess whether randomisation was conducted adequately, or whether concealment of allocation was adequate due to lack of information reported in the study publications. This raises the possibility of selection bias.

3.1.7.3 Statistical NMA methods

The company used two different statistical methods to conduct the NMA. One was a Bayesian NMA using constant hazard ratios (assuming proportional hazards). The other was a Bayesian time-varying hazard ratio model using fractional polynomials (CS Appendix D.1.1.5). Both methods were conducted as it was not known in advance which would provide the best combination of fit and parsimony (CS Section B.2.9.2). The company subsequently chose the constant hazard ratios NMA as their primary (base case) analysis (see below for a discussion of this).

The Bayesian constant hazard NMA was performed using a fixed effect regression model as described in the NICE Decision Support Unit technical support document number 2. The justification for using fixed rather than random effects model was that the network was sparse

and this model did not yield a stable estimate of the heterogeneity parameter, generating unrealistically wide credible intervals (CS section D.1.1.5). Fixed effects assume there is no variation in relative treatment effects across studies for a particular pairwise comparison. The ERG notes that a random effects model is required in the presence of heterogeneity and is a more conservative approach (it generates wider confidence/credible intervals). However, the company did not assess statistical heterogeneity as most of the comparisons in the network are informed by only a single trial. Heterogeneity arising from pairwise comparisons would therefore not be applicable. For transparency the ERG requested the company to supply NMA results based on the random effects model (clarification question A17). The company supplied these but urged caution since the estimated HRs were not considered to be stable as a result of the available data being too limited to estimate the between-study heterogeneity. The ERG notes that the random effects HRs are almost identical to the fixed effect model (as would be expected), but the credible intervals are very wide. Taking into account the sparse network and the wide intervals generated, the ERG therefore agrees that the fixed effect model is appropriate for use in this case.

3.1.7.4 Fractional polynomial NMA model

The CS cites a publication by Jansen 2011[39] as the basis of their fractional polynomial methodology. Jansen describes this method as an alternative to NMA of survival data in which the treatment effect is represented by a constant HR. A multi-dimensional treatment effect approach is used in which hazard functions of interventions compared in an RCT are modelled, and the difference between the parameters of these fractional polynomials (FPs) within a trial are synthesized (and indirectly compared) across studies. The FP analysis generates results which reflect the time course of the log-hazard function and as such can be expressed as log-hazard function curves and their parameters (intercept and slope). Credible interval curves can be plotted alongside the log-hazard function curves. The ERG notes that, although this is a relatively new methodology, FP-based NMAs have also been included in other NICE STAs, for topics such as urothelial cancer (NICE TA492) and renal cell carcinoma NICE TA591 and TA463[40-42].

For each treatment arm of each trial in the company's NMA, the reported Kaplan-Meier curves were digitized and divided into consecutive intervals over the follow-up period. For each time interval extracted survival proportions were used to calculate the patients at risk at the beginning of that interval and incident number of deaths. A binomial likelihood distribution of the incident events for every interval was assumed.

Two orders of FP model were considered for inclusion: first-order, which corresponds to the Weibull model (where exponent P1=0) or the Gompertz model (where exponent P1=1); and second-order models with exponents P1=0 and P2=0; P1=0 and P2=1; P1=1 and P2=0; and P1=1 and P2=1. The CS did not include a zero-order FP model which the ERG believes would be analogous to a proportional hazards-based model. The ERG requested this from the company (clarification question A15). In response the company ran the NMA using each of the six fractional polynomial models with a treatment effect only on the scale parameter of the log-hazard function (thus assuming proportional hazards). The ERG notes that HRs for OS and PFS generated by this model appear similar to those obtained from the constant hazard ratios NMA.

3.1.7.5 Choice of fractional polynomial NMA model

To select the most appropriate FP model the company used the deviance information criteria (DIC) to compare goodness-of-fit. The DIC is commonly used to compare the fit of Bayesian statistical models. The model with the smallest DIC is estimated to be the model that would best predict a replicate dataset which has the same structure as that currently observed.[43] It appears that the model with the lowest DIC was selected by the company. The CS does not state whether any other considerations were taken into account in the choice of model, such as clinical plausibility with respect to OS and PFS as observed in the constituent trials in the NMA. Responding to a clarification question the company stated that the DIC was the sole criterion to select the statistical model for the NMA (clarification response A14). They commented that this is appropriate as the aim of the NMA is primarily estimation rather than extrapolation of relative treatment effects. For OS the best fitting model selected was the 2nd order (P1=1, P2=0), and for PFS the best fitting model was the 2nd order (P1=1, P2=1).

The ERG requested the NMA results from the company (in terms of PFS and OS HRs and accompanying parameter estimates) for each of the other five FP models (clarification question A15). The company supplied these as requested in their response document and in addition, HRs for all treatments versus MPT at six monthly intervals from 0 to 90 months for all six FP models (not originally provided in the CS). The ERG notes from visual inspection of the FP HR plots (Figures 2 to 7 in the company's clarification response document) that the OS HRs (compared to MPT) appear to be broadly consistent between the six fractional polynomial models (by the slope of the curves). However, there is more variation between fractional polynomial models for the PFS outcome (Figures 8 to 13 in the company's clarification response document), notably for VMP versus MPT which shows a marked increase in HRs over time in the Gompertz fractional polynomial model, the second order fractional polynomial model (P1=1, P2=0) and the

second order fractional polynomial model (P1=1, P2=1), (the latter being the best fitting fractional polynomial model chosen by the company, see CS Figure 16). The HRs reach a peak of between 10 to 12 at the end of the observation period (at 90 months), with very wide credible intervals favouring MPT (Table 19 of the company's response document also reported these as numerical values in addition to curves). The company does not discuss the explanations for and consequences of the differences between the fractional polynomial models. The ERG's interpretation of this is that, for PFS, the results of the fractional polynomial NMA results are sensitive to the model chosen, with much uncertainty around the estimates within some of the fractional polynomial models, including within the best-fitting model selected by the company. This potentially over-estimates the comparative effectiveness of Rd compared to VMP which is demonstrated by lower incremental cost effectiveness ratios (ICERs) when a fractional polynomial rather than a constant HR model is used to inform the comparison of Rd versus VMP – as discussed later in this report (section 4.3.10).

3.1.7.6 Choice between a constant hazard ratio NMA and a time-varying fractional polynomials NMA

Having conducted the two statistical methods the CS states that the constant HRs should be considered for the primary analysis of PFS and OS as the time-varying HRs NMA results did not indicate a statistically significant time-dependency in the HRs.

CS Table 19 and Table 21 provide the basic parameter estimates of the 2nd order FP model selected by the company for OS and PFS, respectively. These tables include the d1 (shape) estimate for each of the treatments included. The company's interpretation of this is that the change in log (HR) was not statistically significant from zero for any comparison and therefore, it is reasonable to assume proportional hazards on this basis. The ERG asked the company to elaborate on the interpretation of the d1 parameter in a fractional polynomial NMA (clarification question A13). The company clarified that d1 is the relative treatment effect on the first shape parameter of the parametric log (HR) function (for each treatment versus MPT). A positive d1 indicates an increasing log (HR) over time, whilst a negative value indicates a decreasing log (HR) over time. Importantly, a value significantly different from zero indicates statistically significant changes in the log (HR) over time. As an example, the OS under the best-fitting 2nd order fractional polynomial model the d1 parameter is -0.00592 for Rd versus MPT, meaning that the HR decreases over time (clarification response, Table 9). This can be observed graphically in CS Figure 15 where the HR line for Rd (in red) decreases over the trial observation period (we reproduce this as Figure 8 later in this report). The d1 credible interval is -0.01212 to 0.00028

and as such includes zero, thus supporting the inference that the d1 parameter value is not statistically significant from zero. The results of the time-varying fractional polynomial NMA, in terms of the basic parameter estimates from the second order fractional polynomial model, are therefore used to justify the company's decision to use the constant hazard ratio NMA.

The ERG notes that the Kaplan-Meier curves for PFS in the MM-020 trial in the CS (Figures 3 to 6 - we reproduce these in section 3.3.1 of this report) diverge after around 92 weeks indicating that the proportion hazards assumption may not necessarily hold. The Kaplan-Meier curves for OS in the MM-020 trial appear more parallel on visual inspection (CS Figure 7 – we reproduce these in section 3.3.2 of this report). The log-cumulative hazards plots of Rd and MPT in the CS (CS Figure 18) for PFS and OS respectively show a similar pattern. This is explained in the CS as a delayed treatment effect for Rd (an increase in the hazard for the fixed duration MPT which was stopped at this point, whereas Rd was given continuously until progression).

3.1.7.7 Summary of the NMA

The NMA includes four trials and was conducted for two outcomes, PFS and OS. The network contains direct comparisons (Rd versus MPT, MPT versus MP, VMP versus MP) and indirect comparisons (VMP versus MPT, VMP versus Rd). However, there are no comparisons informed by both direct and indirect evidence. The results of the indirect comparison of Rd versus VMP are used to inform the economic model. Baseline characteristics were well distributed across the four included trials and the trials appear similar enough to fulfil the assumptions underpinning the NMA (CS section B.3.2.1).

The company conducted two NMA statistical approaches: one based on constant HRs assuming proportional hazards, and one based on time-varying HRs as estimated by a fractional polynomial model (which does not assume proportional hazards). The parameter estimates from the fractional polynomial NMA (specifically d1, the relative treatment effect on the first shape parameter of the parametric log (HR) function) were not statistically significant from zero for any comparison. This indicates that the proportional hazards assumption can be met and supports the company's choice of using constant HRs as their primary analysis. The ERG notes that there is inconsistency between the different fractional polynomial NMA models in the PFS HRs for the comparison of Rd and VMP, with wide credible intervals. Taking all the above issues into consideration, the ERG believes that use of the constant hazard ratio NMA as the primary analysis is appropriate in this instance.

3.2 Summary statement of company's approach

Table 10 provides the ERG quality assessment of the company's systematic review of clinical effectiveness. As the table shows, the systematic review met all of the criteria indicating a good quality systematic review, though with some caveats. In summary, there is a low chance of systematic error in the systematic review based on the methods reported in the CS.

Table 10 Quality assessment - Centre for reviews and dissemination criteria (CRD) of CS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes (ERG critique 3.1.2), although a couple of additional comparators could have been included. The criteria were interventions based on lenalidomide, thalidomide, bortezomib and melphalan plus prednisone as monotherapy or as part of a combination, excluding all other treatments. Comparators were placebo studies, intervention therapies at a different dose or duration and any other active drug provided as monotherapy or as part of a combination therapy. Studies of thalidomide with melphalan and prednisone (MPT) were included, but studies of an alternative regimen comprising thalidomide with attenuated cyclophosphamide and dexamethasone (CTDa) were excluded as they are not licensed in the UK. Expert clinical advice to the ERG is that CTDa is widely used in UK despite not being licensed. It is regarded to be similar in effectiveness. Bortezomib combination of bortezomib, melphalan and prednisone (VMP) were included in the CS, however expert clinical advice to the ERG suggests that other bortezomib regimens such as bortezomib (with cyclophosphamide) and dexamethasone (CVD) are also sometimes used for first line treatment despite not being licensed for first line use in the UK.
2. Is there evidence of a substantial effort to search for all relevant research? i.e. all studies identified	Yes (ERG critique section 3.1.1), although eligibility criteria for interventions and comparators were developed prior to the release of the draft scope and therefore were broader than required for the decision problem. A wide range of electronic databases and other sources were searched (14/3/2016) and searches were subsequently updated twice

	(8/11/2016 and 8/8/2017). The company states that the included studies were narrowed down to those relevant to the decision problem.
3. Is the validity of included studies adequately assessed?	Yes (ERG critique section 3.1.4), standard criteria have been used. CRD criteria are used for the MM-020 trial (CS Appendix D.1.3, Table 66). In addition, the Cochrane Risk of Bias criteria are used to assess bias for three comparator RCTs included in the NMA and also the MM-020 RCT (CS Appendix D.1.3, Table 67). Data from MM-020 was used substantially in the CS to inform the economic model.
4. Is sufficient detail of the individual studies presented?	Yes. Key characteristics are tabulated and reported in the text, accompanied by illustrative figures. Limited baseline data are given for the comparator trials included in the NMA.
5. Are the primary studies summarised appropriately?	Yes, see summary ERG Section 3.4.

3.3 Summary of submitted evidence

3.3.1 Summary of results for progression-free survival (PFS)

Table 11 presents an overview of the PFS analyses presented in the CS for the primary comparisons of Rd versus MPT and their results.

Table 11 Summary of PFS analyses presented in the CS (ITT population) for Rd vs MPT

PFS, median months	Rd (n=535)	MPT (n=547)	Hazard ratio (95% CI), p-value
24th May 2013 data cut-off, IRAC assessment (FDA censoring)	25.5	21.2	0.72 (0.61 to 0.85), p=0.00006
24th May 2013 data cut-off, IRAC assessment (EMA censoring)	27.3	23.4	0.79 (0.68 to 0.92), p=0.00210
21st January 2016 data cut-off, Investigator assessment (FDA censoring)	26.0	21.9	0.69 (0.59 to 0.79), p<0.00001
21st January 2016 data cut-off, Investigator assessment (EMA censoring)	26.5	23.0	0.74 (95% CI 0.65 to 0.85), p=0.00001

Reproduction of CS Table 14.[23 44]

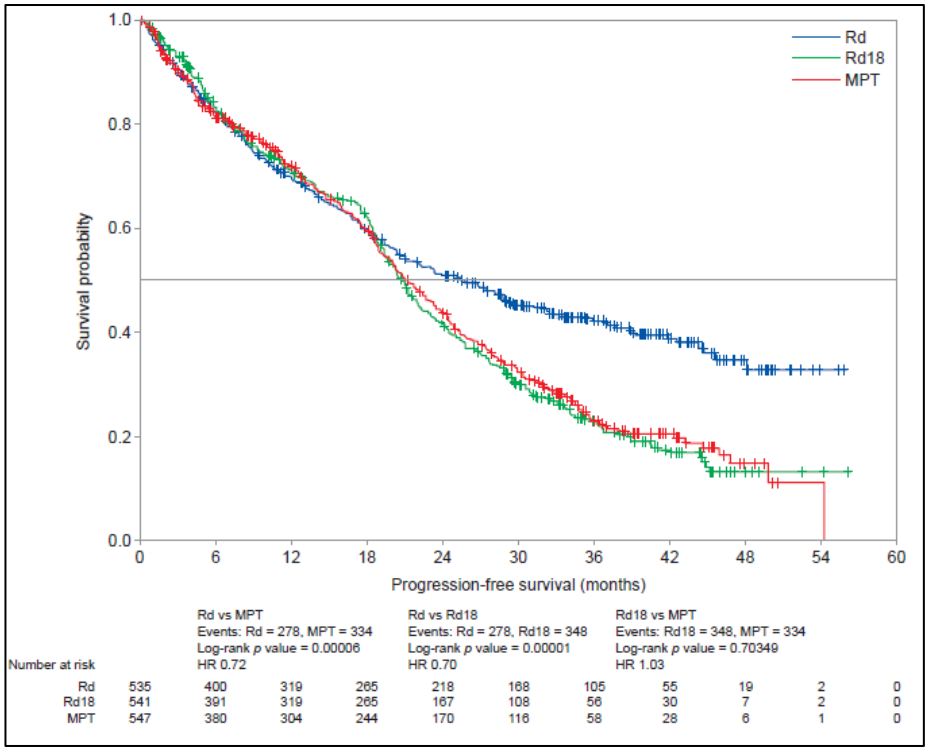
3.3.1.1 Primary outcome - progression-free survival (PFS)

The CS presents the IRAC review (IMWG criteria; FDA censoring criteria)[25] for the planned primary comparison of PFS for Rd vs MPT at 72 weeks duration (May 2013 data cut-off, median

follow-up 37 months). Kaplan-Meier plots for the 24th May 2013 data cut-off showed a 28% reduction in the risk of disease progression or death for Rd (HR 0.72; 95% CI 0.61-0.85; p= 0.000060, with a difference of 4.3 months in median PFS between the groups (25.5 months Rd; 21.2 months MPT) (Figure 2). Patients treated with Rd were more than twice as likely to remain event-free at four years than those treated with MPT (35% Rd; 15% MPT).[23] The ERG requested from the company the investigator assessment of PFS at the 24th May 2013 data cut-off (clarification question A9). These were subsequently provided and showed similar results to the IRAC assessment (results not reproduced here).

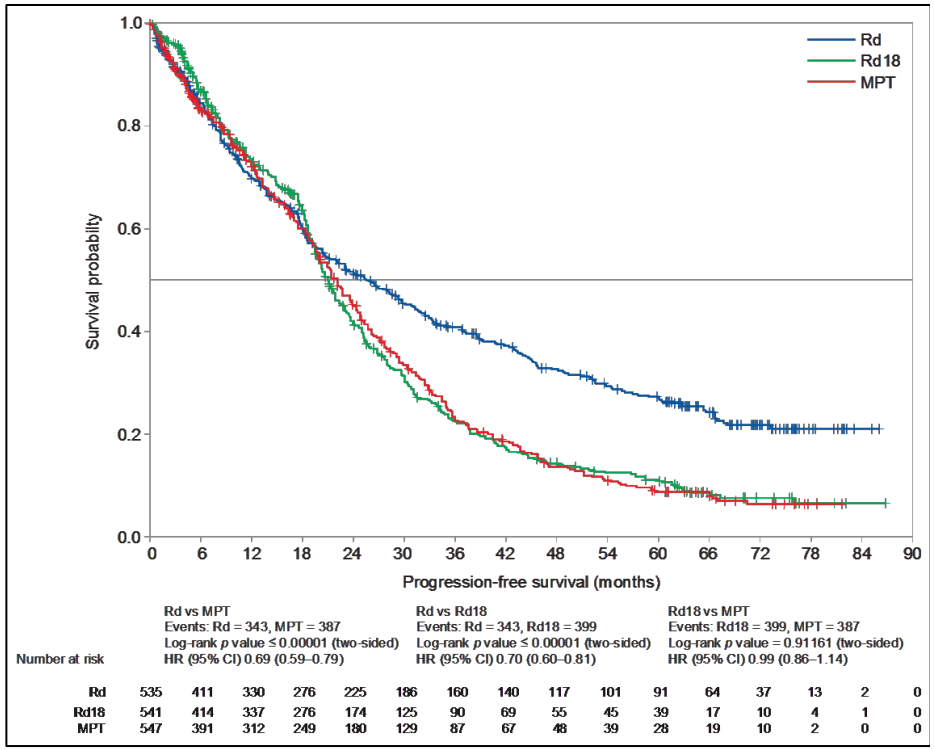
PFS at 72 weeks duration for the secondary PFS comparison between treatment with Rd and Rd18 showed a 30% reduction in the risk of disease progression or death for Rd (HR 0.70; 95% CI 0.60-0.82; p=0.00001). At four years, 35% of patients receiving Rd compared with 13% receiving Rd18 remained event-free.

The CS presented an updated analysis of PFS data based on the later 21st January 2016 data cut-off (Figure 3) by investigator assessment (IMWG criteria; FDA censoring rule), with a median follow up 67 months. Kaplan-Meier PFS plots remained consistent with results from the earlier data cut-off (Figure 2). The Rd group had a 31% lower risk of disease progression or death compared with the MPT group (HR 0.69; 95% CI 0.59 - 0.79; p<0.00001) and 30% compared with the Rd18 group (HR 0.70; 95% CI 0.60 - 0.81; p<0.00001).[23] Median PFS was greatest in the Rd group (Rd = 26 months; Rd18 = 21 months; MPT = 21.9 months). Patients in the Rd group had a 6.9 months longer median TTP (p<0.00001) compared to the MPT group (Rd = 31.3 months vs MPT = 24.4 months), with a 36% lower risk of disease progression or death (HR 0.64, 95% CI 0.54 - 0.75). At five years, the highest proportion of patients remaining event-free were those receiving the continuous lenalidomide combination (27% Rd; 11% Rd18; 9% MPT).



Reproduction of CS Figure 3.[23]
Horizontal line indicates the median; short vertical lines on each curve indicate patients with censored data.

Figure 2 Kaplan–Meier plots of PFS - IRAC review (IMWG criteria), ITT population (FDA censoring criteria). 24th May 2013 data cut-off.

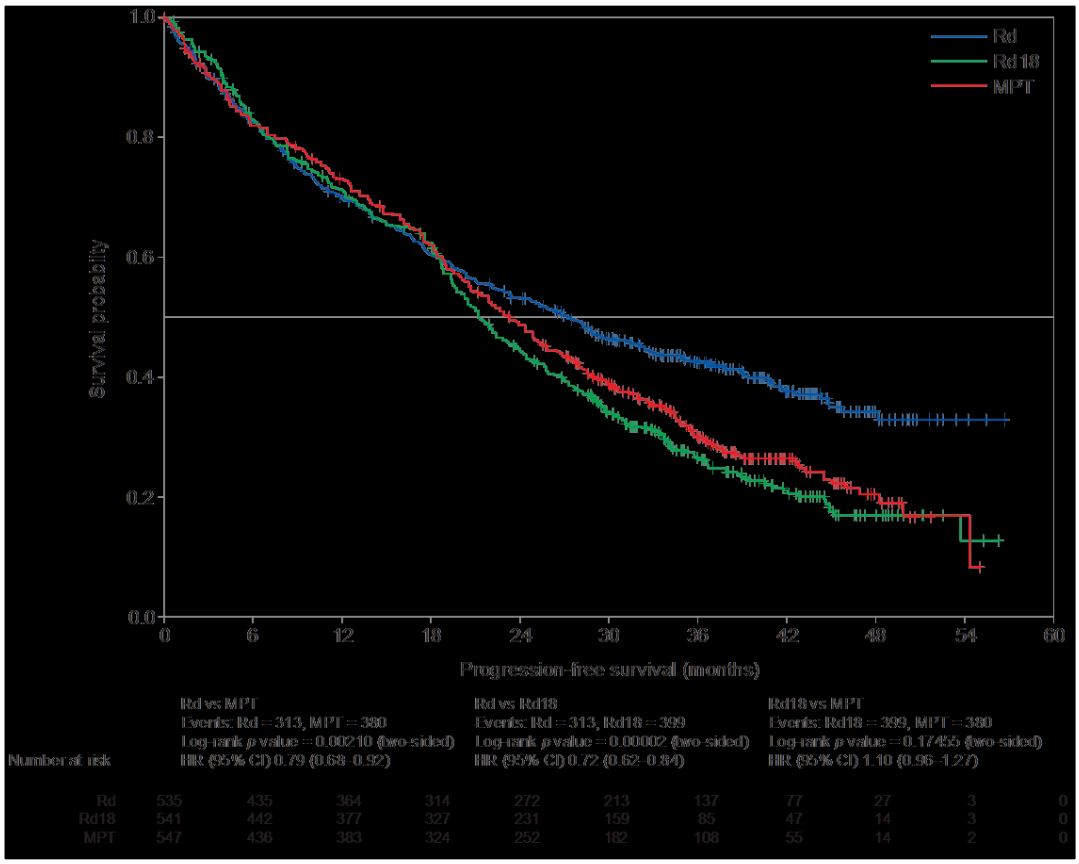


Reproduction of CS Figure 5.[23 44]
Horizontal line indicates the median; short vertical lines on each curve indicate patients with censored data.

Figure 3 Kaplan–Meier plots of PFS - Investigator assessment (IMWG criteria), ITT population (FDA censoring criteria). 21st January 2016 data cut-off.

3.3.1.2 Sensitivity analysis, IRAC assessment (EMA censoring criteria) 24th May 2013 data cut-off

The company presented a sensitivity analyses for PFS by IRAC assessment (IMWG rules) in order to assess the robustness of the primary PFS results (FDA censoring rules) (Figure 4). The data was re-analysed using censoring rules based on 2012 EMA guidance (PFS definition: time from randomisation to objective disease progression or to death from any cause).[45] The results, although more conservative than those based on FDA criteria, were consistent with the primary PFS analysis (HR 0.79; 95% CI 0.68–0.92; p=0.00210).

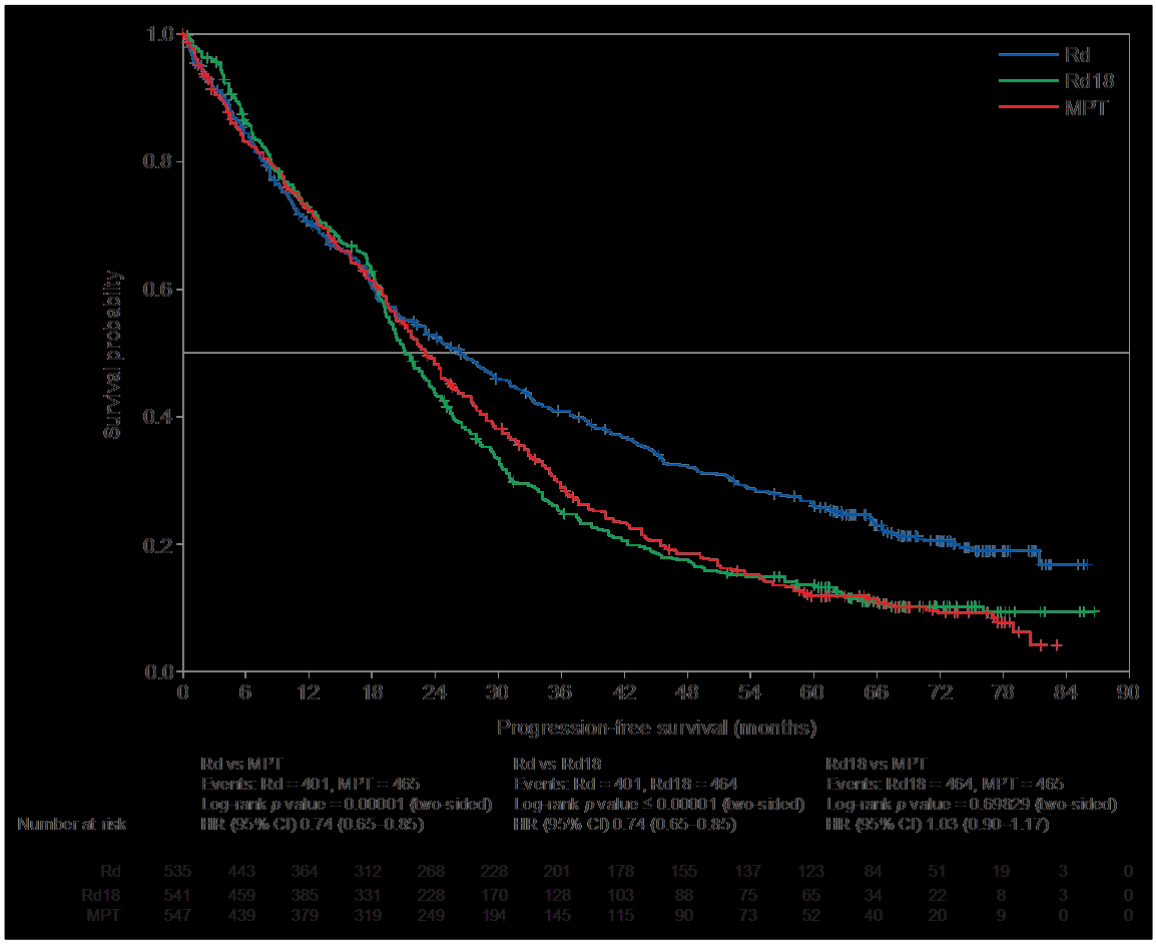


Reproduction of CS Figure 4.[23 44]

Figure 4 Kaplan–Meier plots of PFS - IRAC review (IMWG criteria), ITT population (EMA censoring criteria). 24th May 2013 data cut-off.

Updated 2016 data analysis (21st January 2016 data cut-off) using EMA censoring rules were similarly more conservative compared to the analysis based on FDA censoring rules. The risk of disease progression or death remained lower for Rd compared to MPT (HR 0.74; 95% CI

0.65–0.85; p=0.00001) and for Rd compared with Rd18 (HR 0.74; 95% CI 0.65–0.85; p=0.00001).



Reproduction of CS Figure 6.[23 44]

Figure 5 Kaplan–Meier plots of PFS - Investigator review (IMWG criteria), ITT population (FDA censoring criteria). 21st January 2016 data cut-off.

3.3.1.3 NMA results for PFS

Results from the NMA showed that Rd patients had a lower risk of disease progression or death compared with those receiving MPT (HR 0.74; 95% CrI 0.65-0.85), Rd18 (HR 0.72; 95% CrI 0.63-0.82), and VMP (HR 0.74; 95% CrI 0.52-1.05) (Table 12). The CS also presented PFS time-varying HRs (with EMA-censored MM-020 data) under the best-fitting second order fractional polynomial model (CS Appendix D, Table 65). Results from this model indicate that the HR of Rd relative to MPT decreases over the course of follow-up. The CS states that results

were statistically important at approximately 18 months, but the meaning of this is unclear. In response to a clarification question request (question A12), the company stated from 18 months onwards, the 95% credible interval excludes 1 implying a statistically significant difference favouring Rd. The credible intervals for the HR of VMP relative to MPT are wide and therefore very uncertain, particularly after 24 months (Figure 6).

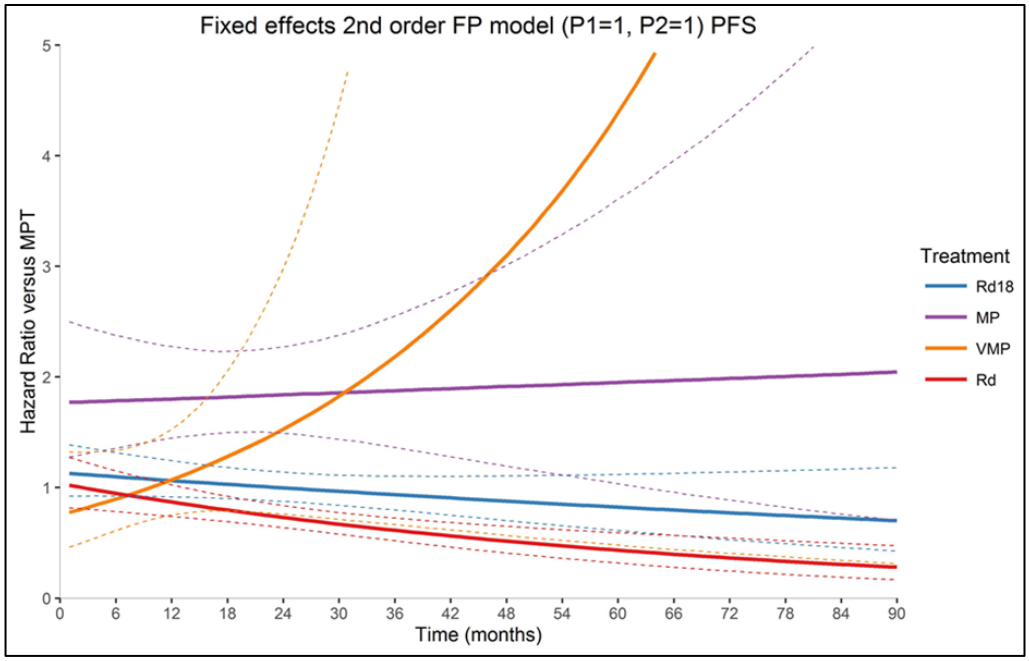
Table 12 Results of fixed effects constant HRs NMA of PFS (with EMA-censored MM-020 data)

MP	**1.79 (1.47, 2.17)**	**2.42 (1.91, 3.06)**	**1.74 (1.37, 2.19)**	**1.79 (1.39, 2.32)**
0.56 (0.46, 0.68)	**MPT**	**1.35 (1.18, 1.54)**	0.97 (0.85, 1.11)	1.00 (0.73, 1.38)
0.41 (0.33, 0.52)	**0.74 (0.65, 0.85)**	**Rd**	**0.72 (0.63, 0.82)**	0.74 (0.52, 1.05)
0.58 (0.46, 0.73)	1.03 (0.90, 1.18)	**1.39 (1.22, 1.59)**	**Rd18**	1.03 (0.73, 1.46)
0.56 (0.43, 0.72)	1.00 (0.72, 1.38)	1.35 (0.95, 1.92)	0.97 (0.68, 1.37)	**VMP**

Reproduction of CS B.2.9.2 Table 20.[44]
Data are presented as the HR (95% CrI). Values correspond to the HR between the row versus the column. Values in bold are statistically significant at the 0.05 significance level.

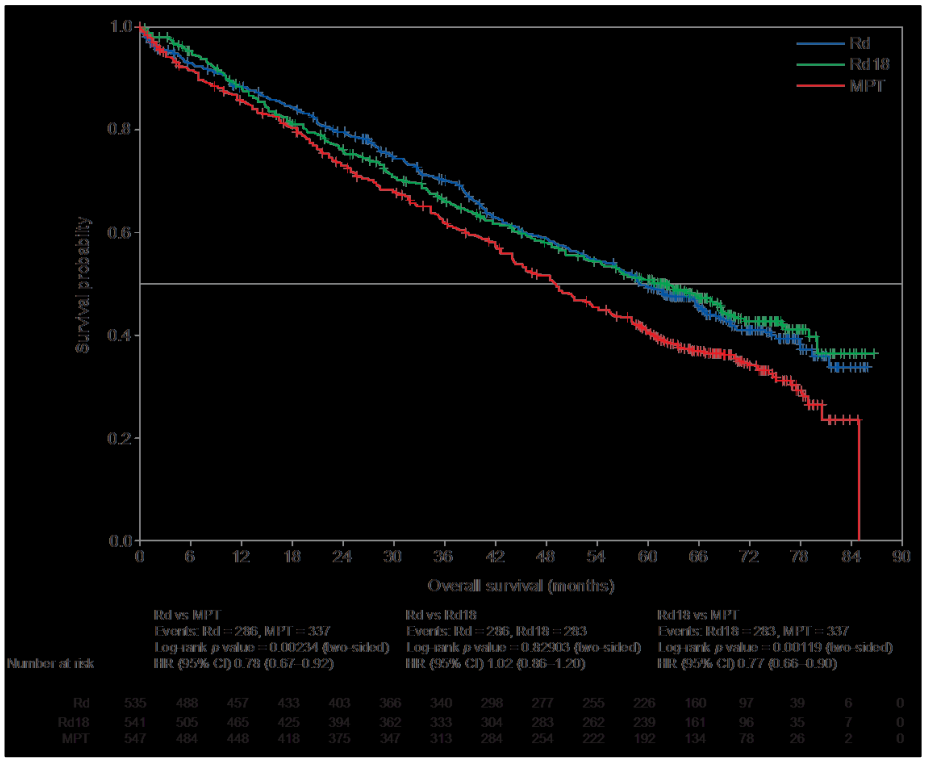
3.3.2 Summary of results for overall survival (OS)

For the secondary outcome of OS, the CS presented the final planned analysis at the 21st January 2016 data cut-off, with a median follow-up time for all surviving patients of 67.0 months.[23] Across treatment groups (ITT population), there were 906 deaths (56%), meeting the pre-specified events for the final OS analysis (n=896) and 623 events (58%) across the treatment groups for Rd versus MPT, also meeting pre-specifications (n=597). Median OS with Rd was significantly longer at 59.1 months compared with 49.1 months with MPT (Figure 7), equalling a 10.0 month improvement for Rd in OS (HR 0.78; 95% CI 0.67-0.92; p=0.002). The estimated five-year OS rates were 8% longer for Rd compared with MPT (49% Rd, 41% MPT).[23]



Reproduction of CS B.2.9.2 Figure 16.

Figure 6 Results of fixed-effects second order fractional polynomial model NMA of PFS with EMA-censored MM-020 data; hazard ratios over time versus MPT



Reproduction of CS Figure 7.

Figure 7 Kaplan–Meier plots of final OS, ITT population. 21st January 2016 data cut-off.

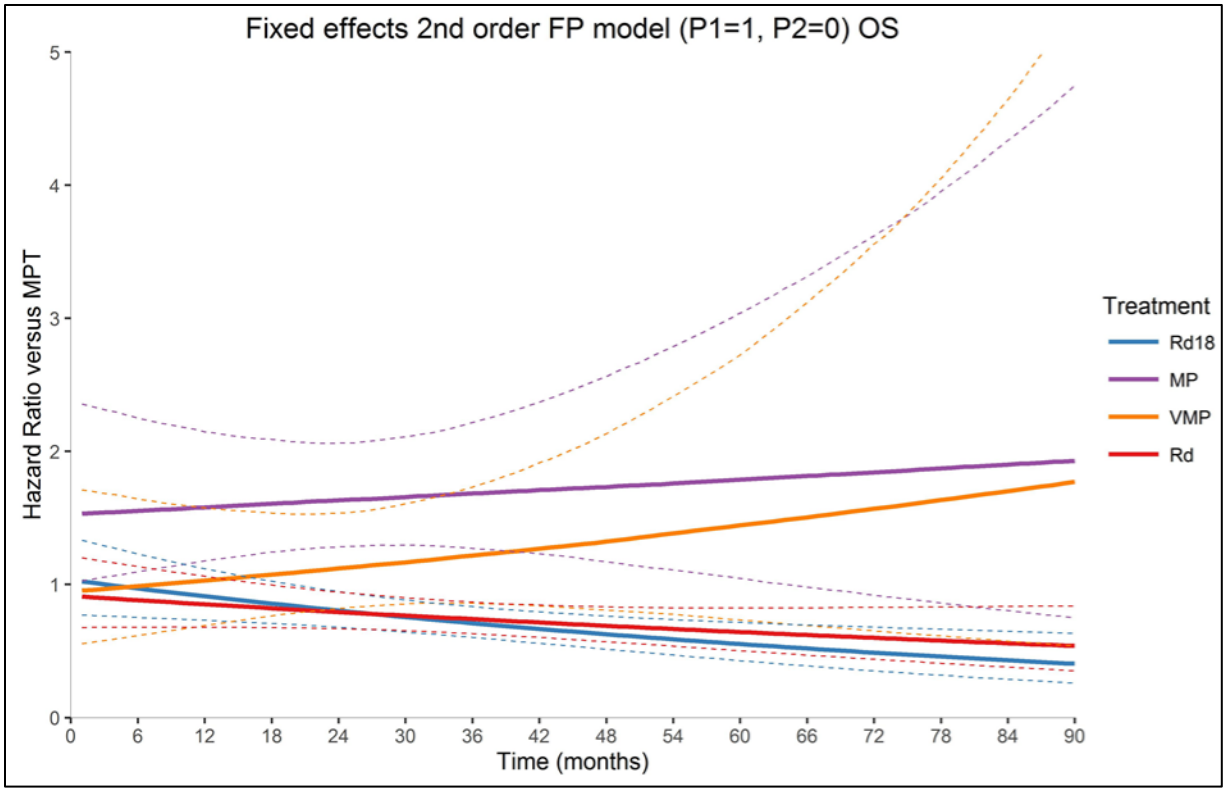
3.3.2.1 NMA results for OS

Results from the NMA estimate indicate a lower risk of disease progression or death for patients treated with Rd compared with MPT (HR 0.78, 95% CrI 0.67 - 0.91) and VMP (HR 0.70, 95% CrI 0.50 - 0.98) (Table 13). Plotted time-varying HRs are presented in Figure 8 (corresponding parameters are reported in CS Table 19 and not reproduced by the ERG). Under the best fitting second order fractional polynomial model (MS Appendix D, Table 64) the HR for Rd versus MPT is lower than 1 from the beginning of treatment and this difference becomes statistically important at approximately 20 months. It is unclear if statistically important equates to statistically significant. In response to a clarification request (question A12), the company stated from 20 months onwards, the 95% credible interval excludes 1 implying a statistically significant difference favouring Rd.

Table 13 Results of fixed effects constant HRs NMA of OS

MP	**1.60 (1.28, 1.99)**	**2.05 (1.56, 2.68)**	**2.08 (1.59, 2.71)**	**1.44 (1.17, 1.76)**
0.63 (0.50, 0.78)	**MPT**	**1.28 (1.10, 1.50)**	**1.30 (1.11, 1.52)**	0.90 (0.67, 1.21)
0.49 (0.37, 0.64)	**0.78 (0.67, 0.91)**	**Rd**	1.01 (0.87, 1.18)	**0.70 (0.50, 0.98)**
0.48 (0.37, 0.63)	**0.77 (0.66, 0.90)**	0.99 (0.84, 1.15)	**Rd18**	**0.69 (0.49, 0.97)**
0.70 (0.57, 0.85)	1.11 (0.82, 1.50)	**1.42 (1.02, 2.00)**	**1.44 (1.03, 2.02)**	**VMP**

Reproduction of CS B.2.9.2, Table 18
Data are presented as the HR (95% CrI). Values correspond to the HR between the row versus the column. Values in bold are statistically significant at the 0.05 significance level.

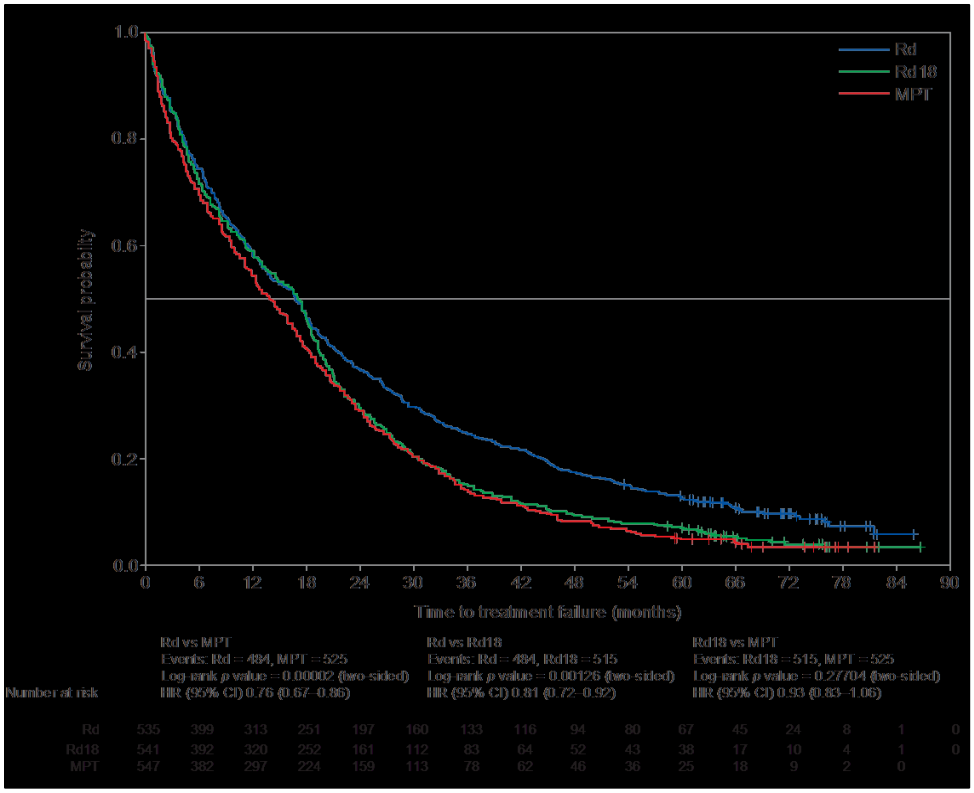


Reproduction of CS B.2.9.2 Figure 15.
MP, melphalan and prednisone; NMA, network-meta analysis; OS, overall survival; Rd, lenalidomide and low-dose dexamethasone until disease progression; Rd18, 18 cycles of lenalidomide and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

Figure 8 Results of fixed-effects second order fractional polynomial model NMA of OS; HRs over time versus MPT

3.3.3 Summary of results for time to treatment failure (TTF)

The CS presented a TTF analysis with a 21st January 2016 data cut-off (Figure 9). TTF with Rd treatment was 2.8 months (median) longer compared with MPT treatment (16.9 months Rd; 14.1 months MPT; HR 0.76; 95% CI 0.67–0.86, p=0.00002). In addition, treatment with Rd showed a 24% reduction in the risk of discontinuing study treatment for any reason compared with MPT (HR 0.76, 95% CI 0.67 - 0.86).[23]



Reproduction of CS Figure 8.
Horizontal line indicates the median; short vertical lines on each curve indicate patients with censored data.

Figure 9 Kaplan–Meier plots of TTF - Investigator assessment, ITT population. 21st January 2016 data cut-off.

3.3.4 Summary of results for tumour response

A greater proportion of patients in the Rd group (80.7%) achieved an ORR than those in the MPT group (67.5%; p<0.00001). Among responders, patients receiving Rd had a faster median time to first response (1.8 months Rd vs 2.8 months MPT; not reported for Rd18) (Table 14) and a statistically significantly longer median duration of response (31.5 months Rd vs 22.1 months MPT; HR 0.61 95% CI 0.51-0.72; p<0.00001) compared with those receiving MPT.

Table 14 Myeloma response rates, 21st January 2016 data cut-off

Parameter	Rd (n=535)	MPT (n=547)	Hazard ratio or Odds ratio (95% CI), p-value
Overall response rate (≥ Partial; response), %[a]	80.7	67.5	OR 2.02 (1.53 - 2.68), p < 0.00001
Median time to first response (months)[a]	1.8	2.8	p = 0.00001

Median duration of response in patients achieving ≥ Partial response[a]	31.5	22.1	HR 0.61 (0.51 - 0.72), p < 0.00001
Response[b], n (%)	**Rd**	**Rd18**	**MPT**
Complete response (CR)	119 (22.2)	110 (20.3)	68 (12.4)
Very good partial response (VGPR)	141 (26.4)	145 (26.8)	99 (18.1)
CR + VGPR	260 (48.6)	255 (47.1)	167 (30.5)
Partial response (PR)	172 (31.6)	170 (31.4)	202 (36.9)
Stable disease (SD)	66 (12.3)	83 (15.3)	116 (21.2)
Progressive disease (PR)	10 (1.9)	6 (1.1)	17 (3.1)
Not evaluable (NE)[c]	27 (5.0)	27 (5.0)	45 (8.2)
CR, VGPR or PR	432 (80.7)	425 (78.6)	369 (67.5)
SD, PD or NE[c]	103 (19.3)	116 (21.4)	178 (32.5)
Comparison between treatment arms[d]			
Rd vs MPT		OR 2.02 (1.53 - 2.68), p < 0.00001[e]	
Rd vs Rd18		OR 1.14 (0.85 -1.54), p = 0.40500[e]	
Rd18 vs MPT		OR 1.77 (1.35 - 2.32), p = 0.00004[e]	

Based on CS tables 14 and 15.

[a] Not reported for Rd18 group; [b] Best response in a patient; [c] Including patients who did not have any response assessment data or not evaluable; [d] It is not clear to the ERG which response measure these ORs are based on; [e] from Fisher's exact test with normal approximation.

3.3.5 Summary results of PFS2 and second-line therapy (21st January 2016 data cut-off)

Fewer patients treated with Rd received second-line therapy compared with patients in the MPT group (55.9% Rd; 69.7% MPT). The CS states that at five years after randomisation, 64% of patients in the Rd group compared with 82% of patients who initially received MPT had gone on to receive a second-line therapy (Appendix B, B.2.6.10). Median PFS2 (defined as time from initial randomisation to second objective progressive disease, start of third-line therapy or death from any cause, whichever comes first) was 7.9 months longer in the patients treated first-line with Rd compared with MPT (42.9 months Rd; 35.0 months MPT; p=0.00003) with a 26% reduction in the risk of PD or death after starting second-line therapy (HR 0.74. 95% CI 0.64 - 0.85). The CS states that these results suggest that the PFS benefit observed with Rd was

maintained with the next line of therapy. As would be expected, more MPT patients received a lenalidomide-based regimen as second line therapy compared to Rd patients (39.4% MPT; 13.7% Rd). The CS states in Appendix L1.1 that the most frequently chosen second-line treatment across treatment groups was a bortezomib-based regimen (59.9% Rd; 44.6% MPT), followed by alkylating agents (51.5% Rd; 23.1% MPT). The CS states that thalidomide-based regimens were seldom used. At the 21st January 2016 data cut-off, a lower proportion of patients in the Rd arm (56%) had received salvage therapy compared to those in the Rd18 or MPT arms (70% each) as can be seen in Table 15.

Table 15 PFS2 and second-line therapy, 21st January 2016 data cut-off

Parameter	**Rd (n=535)**	**MPT (n=547)**	**Hazard ratio (95% CI), p-value**
Median PFS2, months	42.9	35.0	HR 0.74 (0.64 - 0.85), *p* = 0.00003
Median time to second-line AMT, months (%)	36.7 (55.9)	26.7 (69.6)	HR 0.63 (0.54 - 0.73), *p* < 0.00001
Salvage Therapy, n (%)	**Rd (n=535)**	**Rd18 (n=541)**	**MPT (n=547)**
Any salvage therapy (ITT population)	299 (55.9)	377 (69.7)	381 (69.7)
Lenalidomide[a]	75 (25.1)	141 (37.4)	264 (69.3)
Bortezomib/carfilzomib[a]	236 (78.9)	283 (75.1)	277 (72.7)
Thalidomide[a]	67 (22.4)	63 (16.7)	38 (10.0)
Glucocorticoid[a,b]	277 (92.6)	357 (94.7)	357 (93.7)
Alkylating agents[a,c]	213 (71.2)	245 (65.0)	188 (49.3)
Other therapies [a]	93 (31.1)	108 (28.6)	99 (26.0)

Partly based on a reproduction of CS Table 14 and Table 16 [23]
CI, confidence interval; ITT, intention-to-treat.
[a] Percentages were based on the number of patients who received any salvage therapy.
[b] Included betamethasone, deltison, dexamethasone, methylprednisolone, prednisolone, prednisone, and corticosteroid.
[c] Included betamethasone, carmustine, cyclophosphamide, fotemustine, melphalan, chlorambucil, busulfan, dihydroxybusulfan, mechlorethamine, lomustine, semustine, dacarbazine, cisplatin, and carboplatin.

3.3.6 Summary of health related quality of life

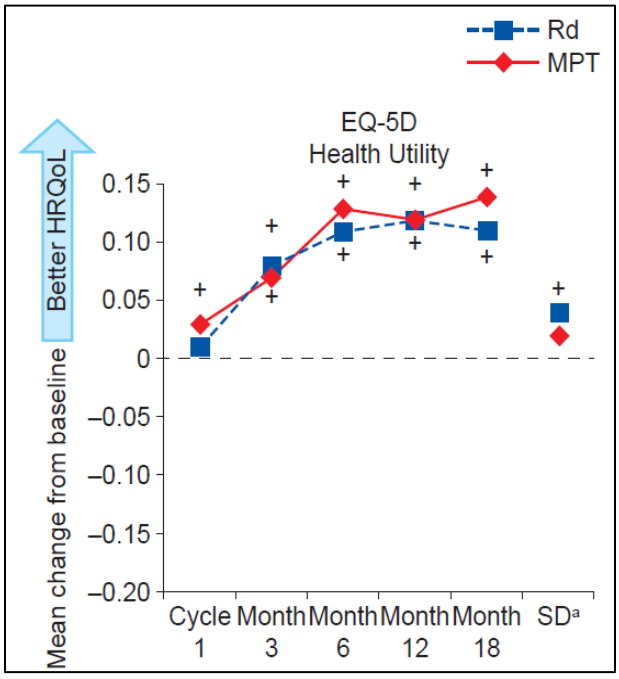
In the MM-020 trial, the HRQoL analysis focused on the generic EQ-5D utility value and six pre-selected and clinically relevant HRQoL domains within the EORTC QLQ-MY20 and the general oncology-related EORTC QLQ-C30 instruments. These six domains included Disease Symptoms and Side Effects of Treatment (QLQ-MY20) and Global Health Status, Physical Functioning, Fatigue and Pain (QLQ-MY30). In order to assess whether statistically significant

differences translated to clinically meaningful differences, the minimal important difference (MID) associated with each domain was considered. For EQ-5D the MID was stated as 0.07 using the Walters and Brazier standard.[46] The source of the MID for the EORTC instruments was not cited however. As stated earlier, the CS pools results for the Rd and Rd18 arms of the MM-020 trial for this analysis. The ERG agrees this is acceptable in this instance. As also stated earlier, EQ-5D results from the MM-020 trial (for the comparison between Rd and MPT) are used to inform the economic model (further detail on this is provided in section 4.3.6 of this report).

The CS reports percentage questionnaire compliance rates at each assessment time point. The exact numbers of patients contributing data, although not quoted in the CS, were available from the journal publication by Delforge et al.[47] Compliance rates were calculated as the number of questionnaire compliant patients divided by the number of patients with clinical data at that assessment timepoint. The CS states that compliance with the questionnaires was similar between treatment arms at the end of the first treatment cycle and after three and six months (≥ 84%). At months 12 and 18 however, compliance rates were statistically significantly lower among patients randomised to MPT than to Rd (around 10% - 15% lower) but at study discontinuation, there was no statistically significant difference between groups, with compliance rates at 53% – 59% between treatment arms.[47]

3.3.6.1 EQ-5D utility value

Results for the EQ-5D are reported in the CS as the mean change from baseline in graphical format, rather than numerically. The absolute EQ-5D values at each assessment time-point are not given. However, the journal publication by Delforge et al.[47] reports that mean EQ-5D utility value at baseline was 0.5 (SD = 0.4) in both treatment arms. The CS reports statistically significant improvements from baseline in patients' EQ-5D HRQoL within both treatment arms, Rd and MPT at all time points after the first cycle ($p < 0.05$). However, no statistically significant differences were reported between treatment arms. Results are summarised in CS Figure 11 which is reproduced below (Figure 10). The CS states that the Rd group demonstrated a consistent clinically meaningful improvement in HRQoL as measured by EQ-5D at all post-baseline assessments except at month one. The CS also states that the MPT group only demonstrated a clinically meaningful improvement at month three. The ERG presumes that the CS is referring to a MID of 0.07 or greater however, from examination of Figure 10 it appears that the MPT group had an increase of HRQoL around 0.07 or greater at all time points except month one.



[+] Significant within-group change from baseline ($p < 0.05$, 1-sample *t*-test).
*Significant between-group difference in change from baseline ($p < 0.05$, 2-sample *t*-test).
[a] Stable disease can occur at any time point.

Figure 10 Cross-sectional analysis of mean EQ-5D change from baseline per assessment visit and at study discontinuation in the Rd and MPT groups for MM-020 (CS Fig 11).

The overall mean change from baseline in EQ-5D utility can be seen from Figure 11 (CS Figure 12). The increase in utility was slightly higher for Rd compared to MPT.

3.3.6.2 EORTC QLQ-C30

Statistically significant improvements (p<0.05) from baseline were observed for Rd and MPT for global health, physical functioning at all time points after the first cycle, however no significant differences were reported between treatment groups.[47] In addition, whilst both Rd and MPT showed statistically significant (p<0.05) reductions in pain at all post-baseline assessments, when the MID of 12 for pain was applied, clinically meaningful improvements at 6 and 12 months for Rd compared to MPT were observed. The Rd group showed statistically significant improvement in fatigue at months 3, 6 and 12 but not at month 18. The MPT group had a statistically significant improvement at months 6 and 12.

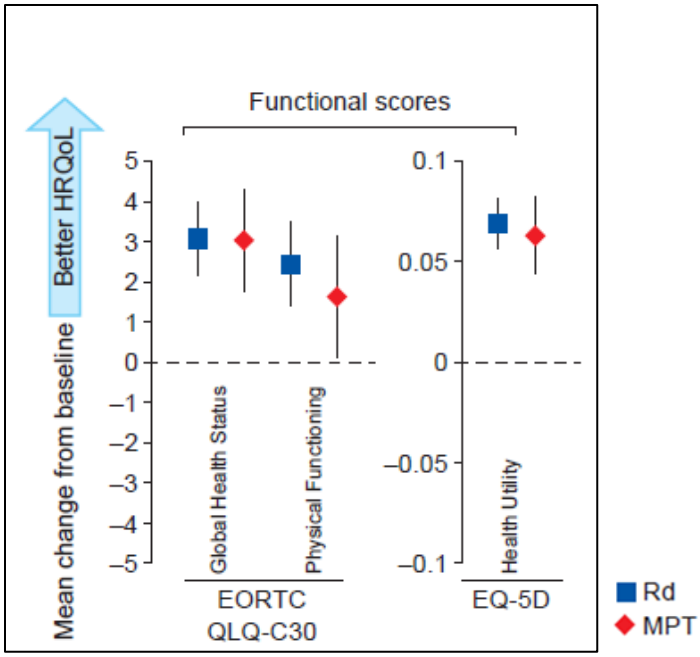


Figure 11 Linear mixed-model repeated-measures analysis of mean change from baseline at 18 months in the Rd and MPT groups for MM-020 (CS Fig 12).

3.3.6.3 EORTC QLQ-MY20

Statistically significant improvements ($p<0.05$) from baseline were also observed for Rd and MPT for the domains of the EORTC QLQ-MY20 questionnaire. Rd demonstrated a significantly greater reduction in disease symptoms compared with MPT at Month 3 ($p=0.04$) and an overall lower symptom score across all assessments.[47] Although Rd and MPT both showed a worsening in the QLQ-MY20 side effects of treatment domain, the Rd group showed consistently lower scores, indicating fewer or less severe side effects, across all post-baseline assessments, with all but month 18 being statistically significantly ($p<0.05$) lower than the MPT group. Results obtained from applying data to a linear-mixed-model repeated measures analysis (CS section 2.6.11) demonstrated a significant difference in mean change from baseline for side effects in the Rd arm versus MPT ($p=<0.0001$). For side effects of treatment, however, with an MID of 6, the results for both Rd and MPT were not deemed to be clinically significant.

3.3.7 Sub-group analyses results

The CS reports investigator assessment of selected outcomes (PFS, PFS2, OS and tumour response) to compare the effect of treatments between specified subgroups.

The CS presents median PFS by age and ISS stage subgroups (Investigator assessment, 21st Jan 2016 cut-off) in Appendix E (CS Table 68). Median PFS was significantly longer for patients under 75 years of age receiving Rd (28.1 months) compared with patients receiving MPT (22.4 months), with a 36% reduction in the risk of disease progression or death for those in the Rd group (HR 0.64, 95% CI 0.54-0.77; p<0.00001). The median PFS for patients with ISS stage I or II multiple myeloma receiving Rd (31.3 months) was also significantly longer compared with those receiving MPT (24.5 months), with a 33% reduction in the risk of disease progression or death for the Rd group (HR 0.67, 95% CI 0.55 - 0.81; p=0.00003) (Table 16).

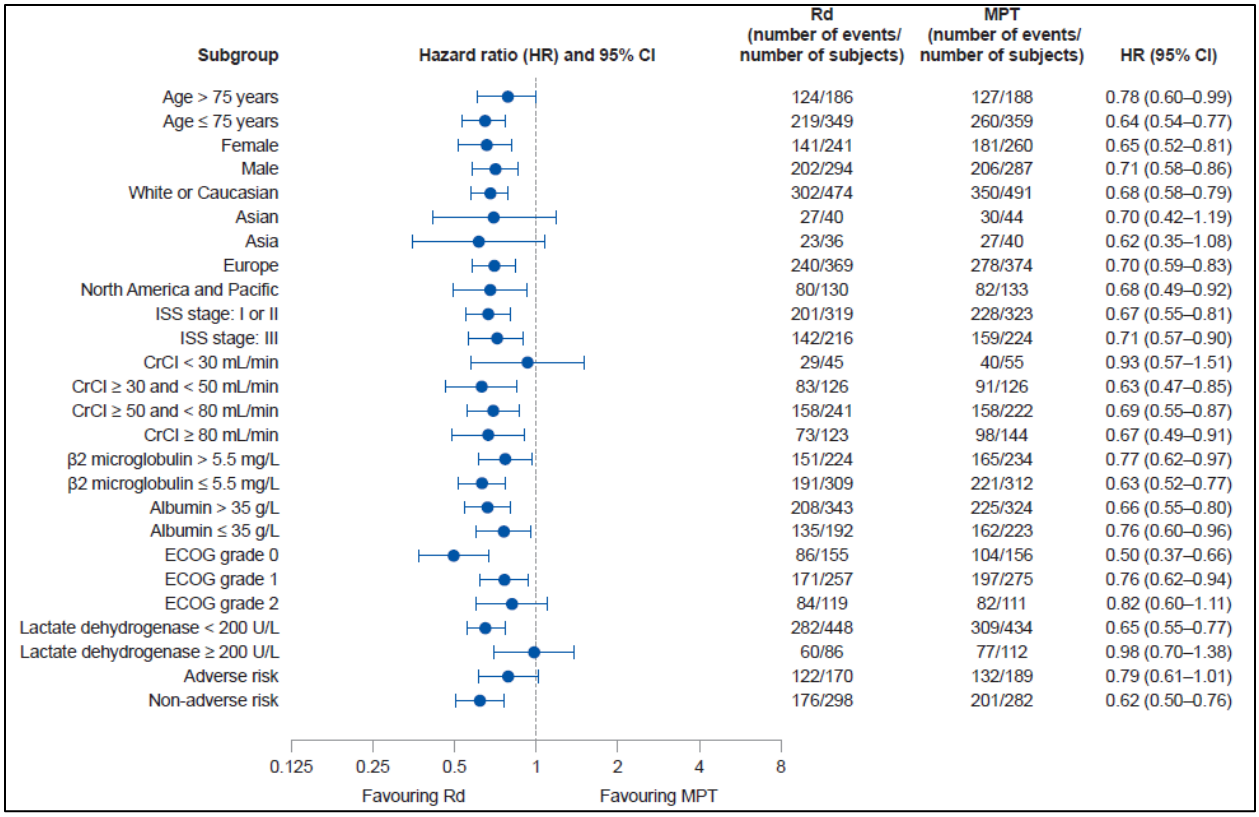
Table 16 PFS by age and ISS stage for MM-020, Investigator assessment –21st January 2016 data cut-off.

Stratification subgroup	Median PFS[a] (months)			HR[b] (95% CI)[c]	p value[d]
	Rd	Rd18	MPT		
≤ 75 years	28.1 (n = 349)	21.6 (n = 348)	22.4 (n = 359)	0.64 (0.54–0.77)	<0.00001
> 75 years	20.3 (n = 186)	19.4 (n = 193)	19.8 (n = 188)	0.78 (0.60–0.99)	0.04454
ISS stage I or II	31.3 (n = 319)	23.1 (n = 322)	24.5 (n = 323)	0.67 (0.55–0.81)	0.00003
ISS stage III	18.4 (n = 216)	18.2 (n = 219)	18.9 (n = 224)	0.71 (0.57–0.90)	0.00414

Reproduction of CS Appendix E, Table 68[23]

[a] Median PFS is based on the Kaplan–Meier estimate.
[b] Rd vs MPT, based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.
[c] 95% CI about the median PFS time.
[d] *p* value is based on the unstratified log-rank test.

Data for the remaining subgroups were presented in a Forest plot (see Figure 12). The CS states that results were consistent with primary ITT analysis showing a benefit for Rd over MPT in the majority of subgroups, except for those with too few patients (e.g. LDH levels ≥ 200 U/L and Asian race).



Reproduction of Figure 33, Appendix E

Figure 12 Hazard ratio by subgroup for PFS between the Rd and MPT treatment arm (ITT Population), Investigator assessment, 21st January 2016 data cut-off

3.3.8 Summary of adverse events

3.3.8.1 Treatment duration and intensity

The CS presents AEs for the MM-020 trial at the 21st January 2016 data cut-off for the safety population (1,613 patients). The median duration of treatment exposure for patients was 80.2 weeks for the Rd group (range 0.7-374.1), 72.0 weeks for the Rd18 group (range 0.9-102.6) and 67.1 weeks for the MPT group (range 0.1-110.0) (CS Section B.2.10.2 and Appendix F, Table 69). The difference in treatment duration between the Rd group and the Rd18 group appears to be primarily related to the study design, in which the treatment arm Rd18 is limited to 18 cycles while Rd continues until disease progression. Treatment duration for over a third of patients in the Rd group (39%) ranged between two and three years, for around a quarter (26%) of patients between three and four years and around a fifth of patients (18%) between four and five years. A small proportion of patients (6%) were treated for more than six years (CS B.2.10.2 and Appendix F, Table 69). Therefore half of the Rd group had a treatment duration in excess of three years.

3.3.8.2 Treatment-emergent adverse events (TEAEs)

Table 17 shows the TEAEs that occurred in ≥10% of patients of any grade, and also corresponding Grade 3/4 TEAEs. The majority of patients (>99%) had at least one TEAE regardless of treatment arm. The CS states that AEs were more likely to occur shortly after treatment initiation and decrease in frequency over time. In the Rd group the greatest number of TEAEs at any grade, occurring as individual AEs and experienced in ≥ 10% of patients were diarrhoea (47.2% Rd; 38.5% Rd18), anaemia (45.7% Rd; 35.7% Rd18), constipation (44.2% Rd; 39.3% Rd18), peripheral oedema (41.2% Rd; 31.3% Rd 18), neutropenia (36.7% Rd; 33.0% Rd18) and back pain (34% Rd; 26.9% Rd18). All of the AEs listed in Table 17 were lower in the Rd18 patient group, who experienced a shorter median treatment. In the MPT treatment group, the greatest number of TEAEs at any grade, occurring as individual AEs and experienced in ≥10% of patients were neutropenia (60.6%), constipation (52.7%), anaemia (42.3%), peripheral sensory neuropathy (35.3%) and peripheral oedema (39.7%). Neutropenia and constipation had a far higher occurrence in patients receiving MPT compared with those treated with Rd. In contrast, over a third of patients receiving Rd had vascular disorders compared with just over a quarter of patients receiving MPT (37.4% Rd; 27.4% Rd18; 25.5% MPT). In addition, psychiatric disorders (described as including insomnia, and depression) affected nearly half of the patients receiving Rd compared with around a third of patients receiving MPT (49.6% Rd; 43.3% Rd18; 30.9% MPT). The CS provided no discussion on these differences.

3.3.8.3 Grade 3–4 TEAEs

Over 80% of patients experienced ≥1 grade 3/4 TEAEs (Rd 86.3%; Rd18 80.2%; MPT 88.7). For patients receiving Rd, Grade 3/4 TEAEs were common in patients for the following categories: blood and lymphatic system disorders (44.2% Rd; 39.6% Rd18; 58.2% MPT); infections and infestations (31.6% Rd; 21.9% Rd18; 17.2% MPT); neutropenia (29.5% Rd; 26.5% Rd18; 44.9% MPT); general disorders and administration site conditions (26.1% Rd; 23.3% Rd18; 19.6% MPT); nervous system disorders (17.9% Rd; 10.7% Rd18; 30.3% MPT); anaemia (18.8% Rd; 15.7% Rd18; 18.9% MPT), and vascular disorders (10.9% Rd; 6.5% Rd18; 6.5% MPT).

Table 17 TEAEs that occurred in ≥ 10% of patients of any grade listed in descending order of frequency of system organ classes for the Rd group and corresponding Grade 3/4 TEAEs (safety population)

Treatment arm / System Organ Class, n (%)	Rd, (n = 532)		Rd18 (n = 540)		MPT (n = 541)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Patients with ≥ 1 AE	**529 (99.4)**	**459 (86.3)**	**536 (99.3)**	**433 (80.2)**	**539 (99.6)**	**480 (88.7)**
General Disorders and Administration Site Conditions	**446 (83.8)**	**139 (26.1)**	**430 (79.6)**	**126 (23.3)**	**423 (78.2)**	**106 (19.6)**
Oedema (peripheral)	219 (41.2)	18 (3.4)	169 (31.3)	10 (1.9)	215 (39.7)	16 (3.0)
Fatigue	180 (33.8)	42 (7.9)	177 (32.8)	46 (8.5)	154 (28.5)	31 (5.7)
Asthenia	155 (29.1)	45 (8.5)	123 (22.8)	33 (6.1)	125 (23.1)	32 (5.9)
Pyrexia	125 (23.5)	17 (3.2)	102 (18.9)	7 (1.3)	76 (14.0)	7 (1.3)
Gastrointestinal Disorders	**437 (82.1)**	**82 (15.4)**	**411 (76.1)**	**58 (10.7)**	**412 (76.2)**	**67 (12.4)**
Diarrhoea	251 (47.2)	25 (4.7)	208 (38.5)	18 (3.3)	89 (16.5)	8 (1.5)
Constipation	235 (44.2)	12 (2.3)	212 (39.3)	10 (1.9)	285 (52.7)	29 (5.4)
Nausea	157 (29.5)	5 (0.9)	128 (23.7)	4 (0.7)	165 (30.5)	13 (2.4)
Vomiting	102 (19.2)	4 (0.8)	68 (12.6)	2 (0.4)	109 (20.1)	10 (1.8)
Abdominal pain	73 (13.7)	8 (1.5)	41 (7.6)	6 (1.1)	30 (5.5)	3 (0.6)
Dyspepsia	59 (11.1)	2 (0.4)	28 (5.2)	1 (0.2)	36 (6.7)	0 (0.0)
Dry mouth	38 (7.1)	0 (0.0)	38 (7.0)	0 (0.0)	62 (11.5)	1 (0.2)
Musculoskeletal and Connective Tissue Disorders	**414 (77.8)**	**108 (20.3)**	**367 (68.0)**	**91 (16.9)**	**312 (57.7)**	**77 (14.2)**
Back pain	181 (34.0)	39 (7.3)	145 (26.9)	34 (6.3)	116 (21.4)	28 (5.2)
Muscle spasms	115 (21.6)	3 (0.6)	102 (18.9)	3 (0.6)	61 (11.3)	4 (0.7)
Arthralgia	111 (20.9)	9 (1.7)	71 (13.1)	8 (1.5)	67 (12.4)	8 (1.5)
Bone pain	91 (17.1)	17 (3.2)	77 (14.3)	15 (2.8)	62 (11.5)	14 (2.6)
Pain in extremity	91 (17.1)	9 (1.7)	66 (12.2)	8 (1.5)	61 (11.3)	7 (1.3)
Musculoskeletal pain	72 (13.5)	3 (0.6)	59 (10.9)	5 (0.9)	36 (6.7)	2 (0.4)
Musculoskeletal chest pain	64 (12.0)	6 (1.1)	51 (9.4)	5 (0.9)	39 (7.2)	3 (0.6)

Infections and Infestations	**402 (75.6)**	**168 (31.6)**	**377 (69.8)**	**118 (21.9)**	**305 (56.4)**	**93 (17.2)**
Bronchitis	97 (18.2)	10 (1.9)	59 (10.9)	6 (1.1)	43 (7.9)	3 (0.6)
Nasopharyngitis	90 (16.9)	1 (0.2)	54 (10.0)	0 (0.0)	33 (6.1)	0 (0.0)
Urinary tract infection	80 (15.0)	9 (1.7)	63 (11.7)	8 (1.5)	41 (7.6)	3 (0.6)
Pneumonia	76 (14.3)	49 (9.2)	68 (12.6)	45 (8.3)	40 (7.4)	31 (5.7)
Upper respiratory tract infection	74 (13.9)	4 (0.8)	53 (9.8)	8 (1.5)	31 (5.7)	3 (0.6)
Nervous System Disorders	**378 (71.1)**	**95 (17.9)**	**333 (61.7)**	**58 (10.7)**	**429 (79.3)**	**164 (30.3)**
Peripheral sensory neuropathy	113 (21.2)	6 (1.1)	93 (17.2)	2 (0.4)	191 (35.3)	51 (9.4)
Dizziness	89 (16.7)	4 (0.8)	70 (13.0)	4 (0.7)	115 (21.3)	16 (3.0)
Paraesthesia	88 (16.5)	0 (0.0)	74 (13.7)	0 (0.0)	103 (19.0)	14 (2.6)
Headache	81 (15.2)	3 (0.6)	52 (9.6)	2 (0.4)	56 (10.4)	5 (0.9)
Tremor	76 (14.3)	5 (0.9)	73 (13.5)	4 (0.7)	100 (18.5)	9 (1.7)
Neuropathy peripheral	35 (6.6)	12 (2.3)	22 (4.1)	5 (0.9)	62 (11.5)	21 (3.9)
Blood and Lymphatic System Disorders	**355 (66.7)**	**235 (44.2)**	**325 (60.2)**	**214 (39.6)**	**423 (78.2)**	**315 (58.2)**
Anaemia	243 (45.7)	100 (18.8)	193 (35.7)	85 (15.7)	229 (42.3)	102 (18.9)
Neutropenia	195 (36.7)	157 (29.5)	178 (33.0)	143 (26.5)	328 (60.6)	243 (44.9)
Thrombocytopenia	111 (20.9)	48 (9.0)	100 (18.5)	43 (8.0)	135 (25.0)	60 (11.1)
Leukopenia	66 (12.4)	25 (4.7)	60 (11.1)	30 (5.6)	94 (17.4)	53 (9.8)
Lymphopenia	60 (11.3)	31 (5.8)	43 (8.0)	18 (3.3)	71 (13.1)	37 (6.8)
Respiratory, Thoracic and Mediastinal Disorders	**314 (59.0)**	**90 (16.9)**	**259 (48.0)**	**53 (9.8)**	**246 (45.5)**	**54 (10.0)**
Cough	129 (24.2)	4 (0.8)	94 (17.4)	1 (0.2)	68 (12.6)	3 (0.6)
Dyspnoea	121 (22.7)	32 (6.0)	89 (16.5)	22 (4.1)	113 (20.9)	18 (3.3)
Metabolism and Nutrition Disorders	**309 (58.1)**	**131 (24.6)**	**274 (50.7)**	**87 (16.1)**	**192 (35.5)**	**62 (11.5)**
Decreased appetite	131 (24.6)	16 (3.0)	115 (21.3)	7 (1.3)	72 (13.3)	5 (0.9)
Hypokalaemia	106 (19.9)	45 (8.5)	62 (11.5)	20 (3.7)	38 (7.0)	11 (2.0)
Hyperglycaemia	64 (12.0)	28 (5.3)	52 (9.6)	23 (4.3)	19 (3.5)	9 (1.7)
Hypocalcaemia	62 (11.7)	25 (4.7)	56 (10.4)	19 (3.5)	31 (5.7)	8 (1.5)

Skin and Subcutaneous Tissue Disorders	**298 (56.0)**	**53 (10.0)**	**276 (51.1)**	**47 (8.7)**	**217 (40.1)**	**38 (7.0)**
Rash	120 (22.6)	33 (6.2)	131 (24.3)	28 (5.2)	93 (17.2)	28 (5.2)
Psychiatric Disorders	**264 (49.6)**	**39 (7.3)**	**234 (43.3)**	**34 (6.3)**	**167 (30.9)**	**14 (2.6)**
Insomnia	150 (28.2)	4 (0.8)	127 (23.5)	6 (1.1)	53 (9.8)	0 (0.0)
Depression	67 (12.6)	10 (1.9)	46 (8.5)	4 (0.7)	30 (5.5)	1 (0.2)
Vascular Disorders	199 (37.4)	58 (10.9)	148 (27.4)	35 (6.5)	138 (25.5)	35 (6.5)
Deep vein thrombosis	55 (10.7)	29 (5.5)	36 (6.7)	20 (3.7)	20 (3.7)	14 (2.6)
Hypotension	57 (10.7)	11 (2.1)	35 (6.5)	8 (1.5)	36 (6.7)	6 (1.1)
Eye Disorders	**183 (34.4)**	**51 (9.6)**	**126 (23.3)**	**22 (4.1)**	**86 (15.9)**	**7 (1.3)**
Cataracts	87 (16.4)	37 (7.0)	31 (5.7)	14 (2.6)	5 (0.9)	3 (0.6)
Investigations	**182 (34.2)**	**55 (10.3)**	**173 (32.0)**	**36 (6.7)**	**142 (26.2)**	**30 (5.5)**
Weight decreased	74 (13.9)	11 (2.1)	78 (14.4)	4 (0.7)	48 (8.9)	4 (0.7)

Reproduction of CS Table 22 (System Organ Classes and Preferred Terms are coded using MedDRA version 15.1).

The CS states that incidence of grade 3/4 TEAEs stratified according to age (≤ 75 years and > 75 years) showed similar rates among treatment groups for patients >75 years of age (89.2% Rd; 85.4% Rd18; 87.5% MPT). Compared to this age group, rates were lower in patients aged ≤75 years receiving Rd, but not in those receiving MPT (84.7% Rd; 77.3% Rd18; 89.4% MPT) This CS states that reported results of pattern and types of TEAEs for the two age groups were reflective of the overall ITT populations.

3.3.8.4 Serious adverse events (SAE)

Treatment-emergent SAEs were reported as occurring in ≥ 1% of patients (CS Appendix F, Table 70 – table not replicated by the ERG) and were over 20% higher in patients receiving Rd (71.1% Rd; 57.0% Rd18; 49.9% MPT). The most frequently reported SAEs occurring in ≥ 1% of patients were infections and infestations (33.1% Rd; 23.7% Rd18; 16.5% MPT), pneumonia (11.1% Rd; 8.9% Rd18; 6.5% MPT) and sepsis (3.2% Rd; 1.9% Rd18; 1.5% MPT). The CS states that the majority of treatment-emergent SAEs were reported with frequencies of 3% or less, with the exception of pneumonia (Rd 11.1%; Rd18 8.9%; 6.5% MPT), pulmonary embolism (3.8% Rd; 2.8% Rd18; 3.1% MPT) and deep vein thrombosis (3.6 Rd; 2.0% Rd18; 1.5% MPT).

The CS suggests that the higher frequency of treatment-emergent SAEs in the Rd group is reflective of the longer drug-exposure time in this treatment arm, which was around 8 weeks longer compared to the Rd18 group and around 13 weeks longer that the MPT group based on medians (see 'treatment duration and intensity' above). The CS states that most AEs occurred within the first 18 months of treatment with continuous Rd, decreasing over time with the exceptions of infections, which remained stable and the development of cataracts, which increased with treatment beyond 18 months. Continuing Rd beyond 18 months was associated with only a small increase in AEs compared with stopping treatment after 18 cycles.

3.3.8.5 Second primary malignancies

Around 12% of all the patients in the safety population experienced at least one second primary malignancy (192/1,613), with similar proportions in the treatment groups (11.5% Rd; 11.1% Rd18; 13.1% MPT (CS Appendix F, Table 71). At the 21st January 2016 data cut-off, the median follow-up time for surviving patients is reported as 67.1 months (range 0.1 - 86.8 months). Haematological malignancies, although low, were higher in the MPT group than in the Rd groups (2.6% MPT; 0.8% Rd; 0.4% Rd18) and invasive second primary malignancy were over 2% higher than in the Rd group (8.5% MPT; 6.8% Rd; 7.0 Rd18).

3.3.8.6 Death

Fewer patients receiving Rd died (53.4% Rd, 52.4% Rd18) at the January 2016 data cut-off when compared with patients receiving MPT (62.1%). The CS reports, the most common cause of death was multiple myeloma (19.9% Rd; 23.5% Rd18; 27.5% MPT). Other reported common causes of death were infections (9.2% Rd; 5.7% Rd18; MPT 8.5%) and cardiac disorders (5.8% Rd; 5.2% Rd18; 3.7% MPT).[23]

3.3.8.7 Treatment discontinuations, dose reductions and dose interruptions

The CS states that most treatment discontinuations occurred due to disease progression regardless of treatment arm (50.7% Rd; 66.9% Rd18; 61.6% MPT). Discontinuation rates due to AEs were similar across treatment arms (12.0% Rd; 13.1% Rd18; 13.9% MPT). Discontinuations due to TEAEs of lenalidomide or thalidomide occurred in over 25% of patients in both the Rd and the MPT treatment group (25.6% Rd; 17.2% Rd18; 27.0% MPT). Dose interruptions were around a third higher in both the Rd and MPT treatment group and around double in the Rd18 group (68.0% Rd; 55.7% Rd18; 71.9% MPT) compared to dose reductions (41.4% Rd; 28.7% Rd18; 47.0% MPT). Both dose interruptions and dose reductions were more common in patients receiving MPT. The MPT treatment group also had higher discontinuations due to AEs in the nervous system disorders system organ class compared to the lenalidomide treatment groups (3.6% Rd; 1.9% Rd18; 12.6% MPT). Peripheral sensory neuropathy was the only specific individual AE that led to discontinuation of a study drug in more than 2% of patients, at 6.7% in the MPT group.

4 COST EFFECTIVENESS

4.1 Overview of company's economic evaluation

The company's submission to NICE includes:

- a review of published economic evaluations of immunomodulatory drugs for patients (≥ 18 years) with untreated newly diagnosed multiple myeloma ineligible for stem cell transplantation and/or older than 65 years of age.
- a report of an economic evaluation undertaken for the NICE STA process. The cost effectiveness of Rd is compared with MPT. For people who are unable to tolerate or have contraindications to thalidomide, Rd is compared with VMP.

The CS proposes that VMP should be considered as the most relevant comparator for the purpose of this appraisal. It is stated that "a cost effectiveness case cannot be made against

MPT due to thalidomide's low acquisition cost" (CS page 94). In light of this, the ERG has primarily concentrated its critique on the comparison of Rd versus VMP for the economic analyses.

4.2 Company's review of published economic evaluations

A systematic search of the literature was conducted by the company to identify economic evaluations in patients with untreated newly diagnosed multiple myeloma who are ineligible or for stem cell transplantation (see section 3.1 of this report for our critique of the company's search strategy).

The inclusion and exclusion criteria for the systematic review are presented in Table 72 in CS Appendix G.1.1. To summarise, the company included bortezomib, lenalidomide, melphalan, prednisone and thalidomide within their search criteria. There was no restriction in comparators. In addition to cost outcomes, studies were included if they reported at least one of the following endpoints: clinical outcomes, utilities or quality-adjusted life years (QALYs). Studies that reported cost-effectiveness-, cost-utility-, cost-benefit- or cost-minimisation analyses were included. Studies reporting cost of illness and budget impact analyses were also included. Lastly, English language studies published from the year 1988 onwards were included. The original search was conducted in November 2016 and an updated search was conducted in August 2017.

Six hundred and eighty three studies were identified from screening 849 records identified from the original and the updated searches. Of these, 644 studies were excluded (51 of which were identified and excluded in the original search), mainly as the studies were in a patient population not relevant to the decision problem. Six publications corresponding to five economic studies were included for full review. Of these, three studies were based on multiple myeloma patients who were transplant–ineligible;[48-51] one study[52] included patients who were ineligible for 'high dose chemotherapy' and the patients in the remaining study[53] were not eligible for high-dose chemotherapy with stem cell transplantation and were unable to tolerate or had contraindications to thalidomide. All the studies included patients aged 65 years and older; except the study by Garrison et al.[50] in which patients had an average age of 70 years at treatment initiation. Three studies used partitioned survival models, [48 51 53] while the remaining two used a Markov model for their analyses.[50 52] The five studies included a total of six treatments: MP, MPT, VMP, CTDa and a combination of melphalan, prednisone and lenalidomide followed by lenalidomide maintenance (MPR-R) and Rd. All the studies included

VMP as a treatment option; MP and MPT were included in four studies each. Two studies included CTDa; and MPR-R and Rd were included by one study each.

A summary of the included studies is presented in CS Table 24 and their modelling characteristics are presented in CS Appendix G Table 27. The key aspects of the included studies are extracted and tabulated below in Table 18.

The study by Usmani et al.[51] is the most relevant to this appraisal as it contained a comparison between Rd and VMP. This study conducted a partitioned survival analysis to model newly diagnosed transplant ineligible multiple myeloma patients transitioning through three health states (PFS, post-progression survival, and death) to assess the cost-effectiveness of Rd vs VMP over patients' lifetime. The study was sponsored by the company and the perspective adopted was the US payer. Data for the clinical efficacy were obtained from the VISTA trial[20] and NMA. Costs associated with AE, routine care, monitoring, subsequent treatments were included. The study found Rd to be more cost-effective compared to VMP as it was associated with greater life years and QALYs with similar overall costs. The differences between the study by Usmani et al.[51] and the results of the company's analysis are discussed in more detail in section 4.3.8.2.

The company performed quality assessment of three studies.[48 50 51] However, for the remaining two studies, by Celgene[52] and Janssen-Cilag,[53] the company reproduced the critical appraisal conducted by Picot et al[48] in NICE technology appraisal of bortezomib and thalidomide for first-line multiple myeloma (TA228 [6]). These two studies were submitted as manufacturer evidence in that appraisal. We view this approach as acceptable. In general, the included studies appeared to be of good quality.

The ERG views that the company conducted a thorough systematic search of the existing literature for the cost-effectiveness review. We did not identify any further studies in addition to those identified and included by the company. The evidence from the included studies were synthesised and critiqued using appropriate methodologies. The findings of these studies were used for validation of the company's economic analysis. Further details are presented in section 4.3.8.

Table 18 Summary of the included studies in the cost-effectiveness review

Study ID, year	Patient population	Model type	Health States	Time horizon	Cycle length	Treatments
Picot, 2011[48] [49]	NDMM patients ineligible for ASCT and/or older than 65 years	Partitioned survival model	1) Treatment 2) Post treatment (first treatment until progression) 3) Post progression until death	Lifetime (30 years)	6 weeks	MP CTDa VMP MPT
Garrison, 2013[50]	Untreated transplant-ineligible multiple myeloma patients with an average age of 70 years at treatment initiation	Markov model	1) Stable disease/minimal response 2) Partial response 3) Complete response 4) Treatment-free interval or lenalidomide maintenance 5) Progressive disease 6) Second-line therapy 7) Death	Lifetime (20 years)	Monthly	VMP MP MPT MPR-R
Usmani, 2016[51]	Initial treatment for transplant-ineligible patients with NDMM and/or older than 65 years	Partitioned survival model	1) Progression free-survival 2) Post-progression survival 3) Death	Lifetime	4 weeks	VMP Rd
Celgene, 2009[52]	Multiple myeloma patients who are older than 65 years or are 'ineligible for high-dose chemotherapy'	Markov model	1) Pre-progression without AE 2) Pre-progression with AE 3) Post-progression 4) Death	Lifetime (30 years)	6 weeks	MP MPT VMP
Janssen-Cilag, 2009[53]	Previously untreated multiple myeloma patients not eligible for high-dose chemotherapy with stem cell transplantation (65 years or older) and unable to tolerate or has contraindications to thalidomide	Partitioned survival model	1) Prior to response to treatment 2) Response but no progression 3) Post-progression; 4) Death	Lifetime (30 years)	Not reported	MP CTDa MPT VMP

Source: CS Table 24 and Appendix G Table 81;

4.3 Critical appraisal of the company's submitted economic evaluation

4.3.1 NICE reference case

The NICE reference case requirements have been applied to the submitted economic evaluation in Table 19. The economic evaluation adheres to the NICE reference case.

Table 19 NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Yes	Company's decision problem shown in CS Table 1
Comparator: As listed in the scope developed by NICE	Yes	Company's decision problem shown in CS Table 1. Comparator described as thalidomide in combination with alkylating agent and a corticosteroid; bortezomib in combination with alkylating agent and a corticosteroid. Other comparators that fit this description are available (e.g. CTDa) but have not been included in the CS.
Perspective on costs: NHS and PSS	Yes	CS Table 1
Evidence on resource use and costs: Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	Not explicitly stated in the CS
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Yes	
Type of economic evaluation: Cost utility analysis with fully incremental analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	Yes	Discussed in more detail in section 3.1.
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	25 years
Measuring and valuing health effects: Health effect should be expressed in QALYs. The EQ-5D is the preferred measure of health related quality of life.	Yes	EQ-5D-3L used in the MM-020 trial for MPT and Rd. EORTC QLQ Q30 data mapped to EQ-5D for VMP.
Source of data for measurement of health related quality of life: Reported directly by patients and/or carers.	Yes	
Source of preference data: Representative sample of the UK population	Yes	
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	
Discount rate: 3.5% pa for costs and health effects	Yes	CS Table 25

4.3.2 Model Structure

The company constructed a cost-utility model for treating multiple myeloma patients with Rd, MPT and VMP. The model has a lifetime horizon of 25 years, discounting of 3.5% per annum for costs and health benefits, a 28-day cycle length and applies a half-cycle correction. The perspective of the analysis is the UK NHS. The CS states that the time horizon was sufficiently long to encapsulate all meaningful differences between the treatments compared given that the starting age of patients entering the model was aged 65 years and that only <1% of patients were alive across all the treatment arms at 25 years and 0% were alive at 28 years. The ERG considers the perspective of the model and the choice of time horizon, cycle length and discounting rate as appropriate.

The company developed a hybrid model structure consisting of partitioned survival analysis (for the time-period <92 weeks) and thereafter (i.e. ≥92 weeks) a multi-state Markov model. The CS stated that owing to the inherent structural link between mortality and earlier progression events, it was more appropriate to model PFS and OS using a state transition approach. However, the clinical trial data from MM-020 trial indicated a delayed treatment effect for Rd on PFS which was due to an increase in the hazard for MPT instead of a decrease in the hazard for Rd. This was not the case for OS. The company suggested that the delayed treatment effect could be due to the difference in the treatment duration for Rd (treatment duration of Rd is until toxicity level is unacceptable or progressive disease) and MPT (treatment duration of MPT is up to 12 42-day cycles).

The Markov model consisted of three health states: progression-free, progressive disease and death. Patients enter the model in the progression-free state, and they can remain in that state or transit to either progressive disease or death states. Patients in the progressive disease state can either remain in that state or transition to death. A schematic of the model (CS Figure 17) is shown in Figure 13. The company modelled OS as a function of all individual transitions in which the death rates reflected the proportion of patients in the progressive disease state and the differences in mortality between progression-free and progressive disease patients.

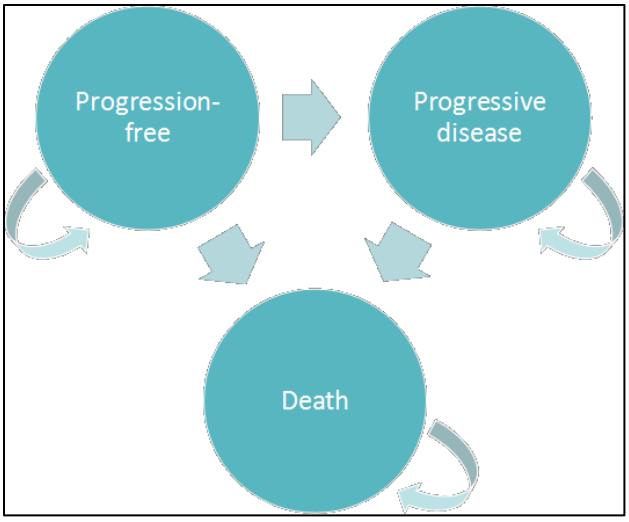


Figure 13 Markov model schematic (CS Figure 17)

Estimates of PFS and OS for VMP within the economic model are from the NMA, as discussed earlier in section 3.1.7. For VMP, OS and PFS were estimated by applying the HRs of VMP versus MPT obtained from the NMA to the MPT PFS and OS curves predicted by the model. The company assumed proportional hazard between MPT and VMP. Further details on modelling treatment effectiveness are discussed later in section 4.3.5 of this report.

Health state utilities were estimated by applying two methods: mixed-effects regression analysis and mapping the EORTC QLQ-C30 values from the VISTA trial to EQ-5D values. The model assumed 'pre-progression utilities' for each treatment to capture the effects of adverse events on HRQoL. Further details are presented in section 4.3.6. Costs associated with drug acquisition and administration (first line and subsequent treatments), adverse events, and laboratory tests and monitoring were estimated (further discussion is in section 4.3.7).

The ERG considers the three state Markov model structure to be an appropriate representation of the biological processes of multiple myeloma and adequately represents the treatment pathway. The company presented a justification as discussed earlier for adopting the multi-state modelling (MSM) technique over a partitioned survival approach to model the clinical outcomes of PFS and OS after 92 weeks. The ERG considers that the company's methodological and structural choices appear to be reasonable overall.

4.3.3 Population

The economic evaluation includes the population defined in the company's decision problem (CS Table 1) as adults with previously untreated multiple myeloma for whom stem-cell transplantation is considered inappropriate. This corresponds with the final scope issued by NICE and the company's marketing authorisation for lenalidomide. The patient population is also consistent with the patient population in the MM-020 trial. However, the company has indicated that their preferred comparison is between Rd and VMP and the ERG notes that VMP is only recommended by NICE for patients who are intolerant or contraindicated to thalidomide. The CS acknowledges that none of the trials in the NMA (including the MM-020 trial) required patients to be intolerant or contraindicated to thalidomide. The CS states that based on clinical advice there are patients with predisposing conditions that make them more susceptible to thalidomide AEs and who would potentially benefit from lenalidomide (e.g. bowel disease, neuropathy, sleep disorders) (CS page 94). The CS therefore considers that use of data from the ITT population of the RCTs in the NMA is appropriate for the cost-effectiveness analysis of lenalidomide in patients who are intolerant or contraindicated to thalidomide. Expert advice to the ERG is that there is no logical reason why the clinical effectiveness outcomes seen for lenalidomide in the MM-020 trial would be different to those seen in patients intolerant or contraindicated to thalidomide. The ERG concludes that the company's approach is therefore reasonable.

4.3.4 Interventions and comparators

The cost-effectiveness analysis compares Rd with MPT and with VMP, as stated in the company's decision problem. MPT and Rd are oral treatments whilst bortezomib is administered subcutaneously. As we have stated earlier, clinical advice to the ERG suggests that CTDa is more commonly used in the UK than MPT as a first line treatment (although it is not licensed for this indication), and is generally considered to be equivalent to MPT in clinical effectiveness.

4.3.5 Treatment effectiveness and extrapolation

The clinical effectiveness evidence used in the company's economic model is from the MM-020 trial for Rd versus MPT and from the company's NMA for the comparison with VMP. We have described the NMA in more detail earlier in section 3.1.7. The main clinical effectiveness outcomes modelled are PFS, OS and TTF.

4.3.5.1 Progression-free and overall survival for Rd and MPT

The company uses a hybrid approach to modelling PFS and OS with a 92-week cut point. For the first 92 weeks the Kaplan-Meier data for the MM-020 trial were used to represent the

proportion of patients in each health state using a partitioned survival methodology. After 92 weeks the MSM model was used. The company justified this approach by stating that the PFS hazard was not constant over time.

The PFS Kaplan-Meier curves from the MM-020 trial for Rd and MPT overlapped until approximately 92 weeks, after which the curves separated (Figure 14). The company produced log-cumulative hazards of PFS for Rd and MPT (CS Figure 18) which showed a divergence of the curves beyond 92 weeks. The company concluded that proportional hazard assumption did not, therefore, appear to hold. The ERG agrees with this conclusion. The company considered that there may be a delayed treatment effect in the trial whereby MPT (and Rd18) treatment arms finish at 72 weeks whilst the Rd arm continues treatment, and PFS curves between Rd and MPT diverge after 92 weeks (i.e. a 20 week 'delay').

The company states that the log-cumulative hazards of OS for Rd and MPT were "not parallel after 92 weeks" (CS page 101). However, the ERG notes that in CS Figure 18, the OS log-cumulative hazards for Rd and MPT do appear parallel after 92 weeks. The ERG therefore considers that for OS the proportional hazard assumption appears to hold.

The company generated transition probabilities for the MSM model using the R statistical software package msm.[54] Transition probabilities were generated for Rd and MPT separately, rather than including treatment as a co-variate, as the proportional hazard assumption did not hold for PFS. The transition probabilities for the MSM model are shown in Table 20 (CS Table 27).

Table 20 MSM probability transition matrices – 28-day probabilities (CS Table 27)

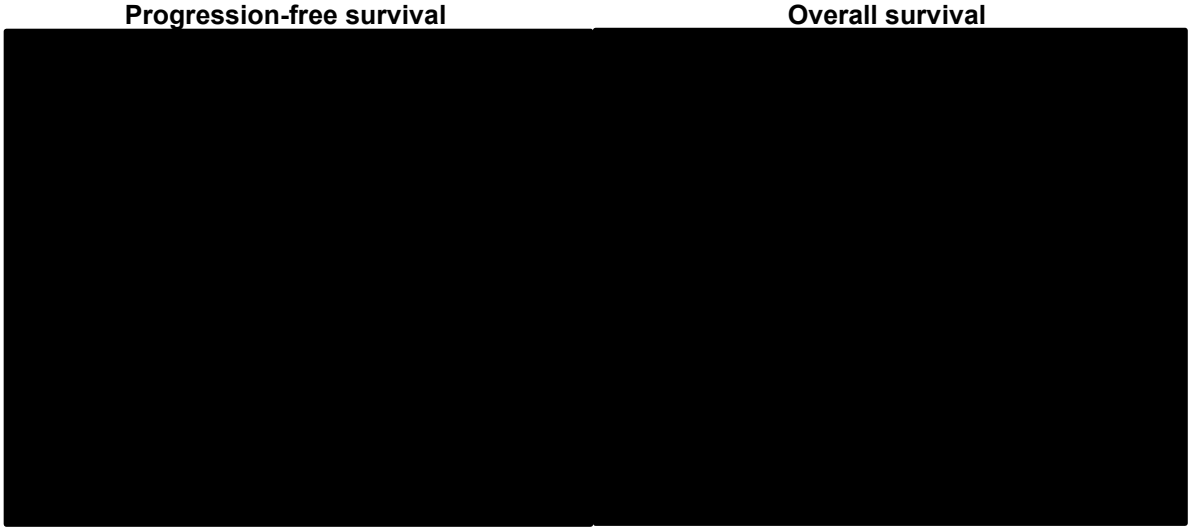
From/to	**Rd**			**MPT**		
	Progression-free	Progressive disease	Death	Progression-free	Progressive disease	Death
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	0	0	1	0	0	1

The CS shows the fit of the MSM to the individual patient data for the following transitions: progression-free to progressive disease, progression-free to death and progressive disease to

death (CS Figure 20). In general, the ERG considers that the plots of the transitions provide a reasonable fit with the Kaplan-Meier data.

The CS provides a comparison between the PFS and OS from the economic model and the Kaplan-Meier data from MM-020 for Rd and MPT (Figure 14 and CS Figure 19). The ERG considers that the modelling approach taken provides a good fit between the economic model and observed Kaplan-Meier data.

Progression-free survival **Overall survival**



Key: ITT, intent-to-treat; KM, Kaplan–Meier; MPT, melphalan, prednisone and thalidomide; MSM, multi-state modelling; Rd; lenalidomide and low-dose dexamethasone until disease progression; trt, treatment.
Notes: Data cut-off = 21st January 2016 (ITT population). The final drop in overall survival is due to the number at risk going from 1 to 0 at 85 months.

Figure 14 Kaplan-Meier plots of survival compared with modelled survival (CS Figure 19)

The company also provides a scenario using time-varying hazards using the fractional polynomials NMA for VMP and Rd versus MPT (CS Table 52). The ERG notes that the scenario with time-varying hazards using fractional polynomials provide a poorer fit to the observed Kaplan-Meier data than by assuming proportional hazards as in the company's base case.

4.3.5.2 Progression-free and overall survival for VMP

In the absence of head-to-head data, VMP is compared to Rd and MPT using the constant HR from the company's NMA applied to the MPT PFS and OS curves. The NMA is described in more detail earlier in section 3.1.7. The mean HRs for VMP versus MPT for PFS and OS are 1.00 and 1.11 respectively. The CS states that MPT was chosen as the reference treatment due to the relative maturity of the MPT data, it also being a fixed-duration therapy and the regimen

also included melphalan and prednisolone. The ERG also notes that MPT is closer than Rd to VMP in the network of trials diagram. The ERG considers that the approach taken is appropriate.

In the company's base case analysis proportional hazards are assumed for VMP versus MPT as the time-varying fractional polynomial NMA did not predict a statistically significant time dependency in the VMP HRs for PFS and OS. However, the CS states that the point estimates of the HR show some "potentially meaningful changes over time" (CS page 105). The company provided a scenario analysis using time-varying HRs using the fractional polynomial NMA (CS Table 52). The ERG's view is that assuming proportional hazards is reasonable approach in this instance. The ERG considers that the scenario using time-varying hazards for VMP appears to produce a less plausible OS curve for VMP than the analysis assuming proportional hazards. In this scenario analysis OS is similar for the VMP and MPT arms for the first two years and thereafter VMP becomes rapidly less effective than MPT.

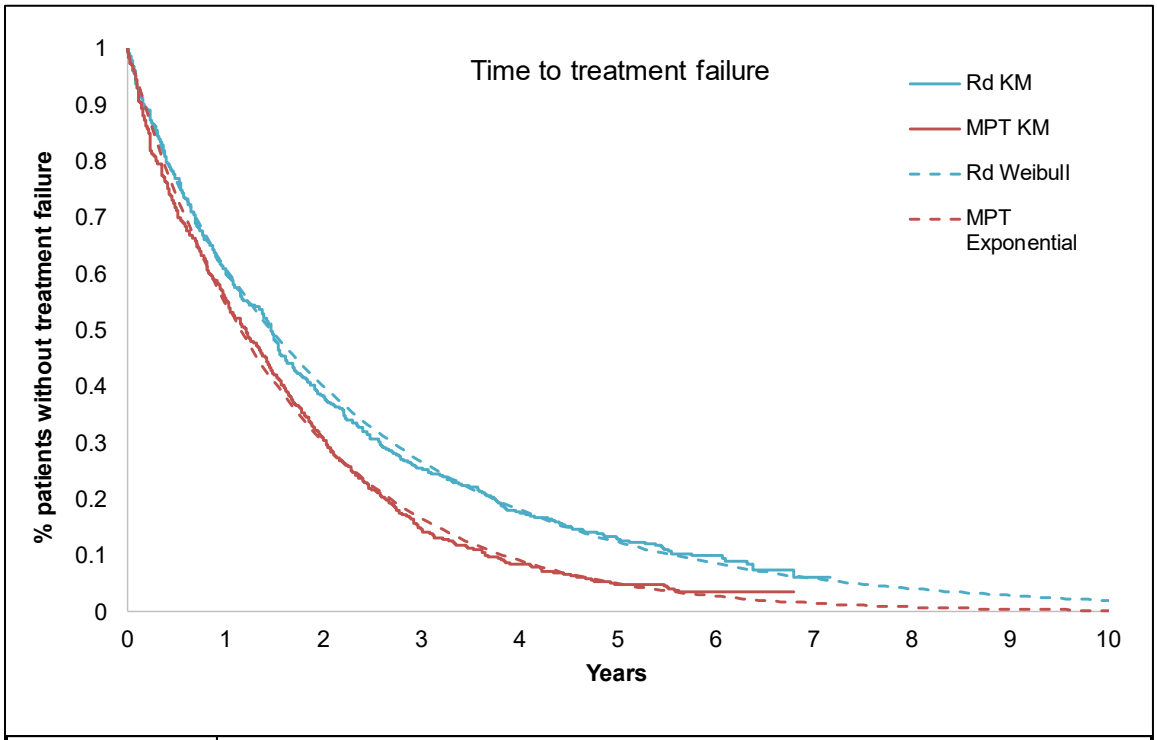
The cost-effectiveness results were most sensitive to changes in the HR for OS for VMP versus MPT (section 4.3.10). Given the uncertainty around the estimate of the HR for VMP versus MPT, the ERG conducts a scenario analysis with a HR=1 of VMP versus MPT for OS (see section 4.4).

4.3.5.3 Time to treatment failure

The proportions of patients on treatment in each model cycle are calculated using patient-level time to treatment failure data from the MM-020 trial. Parametric curves were fitted to the Rd and MPT arms. The Akaike Information Criteria (AIC) and Bayesian Information Criterion (BIC) statistics were used to determine the parametric curve which showed the best fit to the observed data. The AIC and BIC statistics are shown in CS Table 28 for Rd and MPT. The CS states that based on the AIC and BIC statistics the Gompertz, Weibull and exponential distribution are plausible fits for Rd and the exponential and Weibull distributions are plausible fits for MPT. For the base case the company selects the Weibull distribution for Rd and the exponential distribution for MPT. A comparison between the TTF fits and the Kaplan-Meier data in MM-020 is shown in Figure 15 (CS Figure 22). The ERG notes that NICE Decision Support Unit Technical Support Document (TSD) guideline 14 states that the same parametric curve should be fitted for both treatment arms.[55] The ERG therefore suggests that Rd and MPT should both use the same distribution for TTF and the Weibull distribution visually provides a better

overall fit for both Rd and MPT than the exponential distribution. This analysis is explored in the ERG additional scenario analyses (section 4.4).

As there are no available data for TTF for VMP, the company assumes that the TTF curve for VMP is equal to PFS up to the maximum treatment duration (nine 42 day cycles). The ERG considers that assuming the TTF curve for VMP is equal to the PFS curve is inconsistent with the approach taken for Rd and MPT. The company also conduct a scenario analysis varying this assumption (CS Table 52) where they assume all patients receiving VMP receive all nine cycles, i.e. no discontinuations. However, there is also an inconsistency in the approach of modelling TTF for the treatments in this scenario. As PFS for MPT and VMP are similar (HR=1), we consider a better approach is for the TTF curve for VMP to be equal to that of MPT. The ERG explores this in a scenario analysis (section 4.4).



	Number at risk					
Years	0	2	4	6	8	10
Rd	535	204	95	32	0	0
MPT	547	168	46	12	0	0

Note: KM data shown are time to treatment failure; completing all 12 MPT treatment cycles does not count as a failure event.

Figure 15 Time to treatment failure curve fits and KM data (CS Figure 22)

In summary, the ERG considers that the approach the company has taken for modelling PFS and OS is reasonable and that the modelled survival curves show a good fit against the trial data from MM-020 for Rd and MPT. For TTF, the ERG noted a couple of issues. Firstly, the company has used different parametric curves to model TTF for the treatment arms for MPT and Rd. Methodological guidance recommends using the same parametric curve for both treatment arms. Secondly, the assumptions used for modelling TTF for VMP is based on PFS and is inconsistent with the methods used for Rd and MPT.

4.3.6 Health related quality of life

4.3.6.1 Review of health-related quality of life

The company conducted a systematic literature review to identify health state utility values for the economic evaluation. The search strategies used are presented in Tables 86-93 of the CS and we discussed these earlier in this report (section 3.1.1 of this report).

The inclusion criteria used by the company are shown in Table 56 of the CS (Appendix D). The inclusion criteria permitted RCTs of treatment of adults with newly diagnosed or untreated multiple myeloma (ineligible for stem cell transplant or aged 65 years or older) treated with lenalidomide, thalidomide, bortezomib and melphalan plus prednisolone. Studies had to report HRQoL outcomes as health utility index scores. Studies that were not RCTs and those recruiting patients before 1988 were excluded. The ERG notes that omitting other study types may have resulted in some potentially relevant studies being missed.

The company's search found one relevant study by Delforge et al.[47] This study reports the company's HRQoL results from the MM-020 trial for Rd versus MPT. We summarised these results earlier in this report (section 3.3.6).

4.3.6.2 Health-related quality of life from clinical trials

The MM-020 trial collected EQ-5D-3L data (with the UK value set) from patients at several time points: at baseline, at end of cycles 1, 3, 6, 12, and 18 and study discontinuation. Results over time since baseline are shown in CS Figure 11 and are reported earlier in this report (see Figure 10).

The company used a mixed-effects regression model to analyse EQ-5D data in order to provide utility by health state and time for Rd and MPT. The results from the mixed-effects regression

model for patients with non-progressed disease are shown in Table 21. The company has used time quartiles, based on the number of observations over time where:

- Q1: 0 – 4.0 weeks
- Q2: 4.0 – 12.0 weeks
- Q3: 12.00 – 28.86 weeks
- Q4: > 28.86 weeks.

Table 21 Mixed effects regression model results of utility for Rd and MPT (from CS Table 30)

Effect	timeQ	Treatment	Estimate	Lower	Upper
Intercept			0.5189	0.4909	0.5468
timeQ	Q2		0.04964	0.02185	0.07744
timeQ	Q3		0.09003	0.06400	0.1161
timeQ	Q4		0.1266	0.09883	0.1543
timeQ	Q1		0	.	.
treatment		Rd	0.001768	-0.0374	0.04089
timeQ*tx	Q2	Rd	-0.01286	-0.0520	0.02627
timeQ*tx	Q3	Rd	0.01805	-0.0181	0.05416
timeQ*tx	Q4	Rd	0.008863	-0.0295	0.04719

Key: Q, quartile; Rd; lenalidomide and low-dose dexamethasone until disease progression; timeQ, time quartile; tx, treatment.

As seen earlier in Figure 10, the HRQoL for patients during treatment increases over time. Also, Rd patients experienced a slightly higher overall increase in utility compared to MPT, though this difference was not statistically significant. The utility values used in each cycle for Rd and MPT are shown in Table 22. Adverse event disutilities were not included separately in the economic model as the trial-based utilities were assumed to capture the impact of treatment-related adverse events.

The CS states that the values for Rd and MPT are not statistically significantly different (as shown by the lower and upper bound of the treatment coefficient in Table 21). The CS states that this has been included in the base case because adverse event quality of life impacts associated with each treatment are not modelled separately, and this coefficient captures the differences in treatment-specific adverse event disutilities. The CS includes a scenario analysis where the treatment coefficient and interaction terms were removed for the utility calculation (CS Table 52).

Table 22 VMP 'progression-free' utility relative to baseline over time

Cycle (per 4 weeks)	Mapped utility score from the VISTA trial	Change from baseline	Modelled change from baseline		Estimated value for VMP assuming 0.53 at baseline*
			Rd	MPT	
1	0.507	+0.000	+0.000	+0.000	0.521
2	0.527	+0.020	+0.037	+0.050	0.541
3	0.514	+0.007	+0.037	+0.050	0.527
4	0.504	-0.004	+0.108	+0.090	0.517
5	0.536	+0.029	+0.108	+0.090	0.549
6	0.579	+0.072	+0.135	+0.127	0.592
7	0.605	+0.098	+0.135	+0.127	0.619
8	0.621	+0.114	+0.135	+0.127	0.634
Thereafter	0.632	+0.125	+0.135	+0.127	0.645

Notes: *Consistent with the MPT and Rd arms, taken from the MM-020 trial

The ERG considers that it is appropriate to include the treatment coefficient in the base case analysis because advice from our clinical experts indicated that there would be an improvement in treatment-related AEs for Rd compared to MPT.

The ERG notes that after treatment with MPT and VMP has finished, patients treated with Rd continue to have a higher utility value than those patients in the MPT and VMP arms. Clinical advice to the ERG stated that many patients treated with MPT may continue to suffer from residual painful and debilitating neuropathy that sometimes get worse on stopping treatment, which may be due to the cessation of steroids. However, in Figure 10 the EQ-5D scores for MPT are higher than Rd in the last time-point at 18 months. The ERG therefore considers that a better assumption would be for the utility values for patients in all arms to be equal after MPT and VMP treatment have finished. We investigate this scenario in section 4.4.

The ERG also notes that the company has used the incorrect cycle duration for VMP with regard to utility. VMP is administered in 42 day treatment cycles, whereas the utility has been assigned to 28 day cycles. We investigate changing this in a scenario analysis (section 4.4).

There were no utility data using EQ-5D available in the VISTA trial for patients treated with VMP. The company conducted a mapping of the EORTC QLQ-C30 scores to EQ-5D from patients in the VISTA trial using an algorithm by Proskorovsky et al.[56] The CS does not provide a rationale for why they used this algorithm, rather than the two mapping algorithms used in

TA228.[6] The mapped utility scores for VMP are shown in Table 22. In order to maintain consistency with Rd and VMP, these utility scores have been recalibrated to assume a baseline utility value for VMP of 0.53. The company has not included scenarios using alternative mapping algorithms. The ERG does not consider that using alternative mapping algorithms is likely to have a large effect on the model results as the company has recalibrated the mapped values to maintain consistency with Rd and VMP.

The utility for progressed disease was also taken from the mixed-effects regression analysis. The progressed disease utility is 0.557 (unadjusted for age). The company notes that there was only one visit post-progression. The company includes a scenario analysis (CS Table 52) that includes subsequent treatment disutilities in progressed disease using an alternative method of calculating post-progression utility (CS Table 33).

Utilities are adjusted by the average age of the patients in the model using the age-banded utility values from the study of EQ-5D population norms by Kind et al.[57] The utilities are adjusted after two years when the patients move in to the 75+ year age bracket.

The ERG considers that the company's approach to estimating HRQoL used in the economic model follows the NICE reference case: EQ-5D-3L values have been used for the model health states. The company has used utility values for MPT and Rd from the MM-020 trial and so the values used are directly related to the population considered. However, there is uncertainty around the utility values for progressed disease as these were based only upon observations taken on the first outpatient visit post-progression. There is also some uncertainty around the utility values used for VMP as these have been taken from a mapping from EORTC QLQ Q30 to EQ-5D. A further uncertainty, as stated earlier in this report (section 3.1.6), is that the CS does not state how missing HRQoL data were estimated in the ITT analysis of the MM-020 trial.

4.3.7 Resource use and costs

The costs and resources used in the economic model consisted of drug costs, monitoring costs (including outpatient appointments, inpatient care, tests and investigations), health state costs, AE unit costs as well as AE management costs. The company did not perform any additional systematic review of the literature to identify sources for resource use and costs.

4.3.7.1 Drug costs

Rd and MPT are oral treatments with mean treatment cycle lengths of 28 and 42 days respectively (Table 23). Lenalidomide is taken for 21 days in each cycle and dexamethasone is taken for four days per cycle (days 1, 8, 15, and 22). Rd is taken until disease progression or unacceptable toxicity. Thalidomide is taken daily and prednisolone and melphalan are taken on days 1-4 of each treatment cycle. MPT is taken for a maximum of 12 42-day cycles (72 weeks). As Rd and MPT are oral treatments, there are no administration costs incurred.

VMP is administered subcutaneously in the outpatient setting for nine 42 day cycles. Bortezomib is administered for eight doses per cycle for the first four cycles and then four doses per cycle for the subsequent five cycles. There is an administration cost of £253 for the first administration of VMP and £361 for subsequent administrations.[58] The ERG notes that the administration cost is based on the Daycase and Reg Day/Night Healthcare Resource Groups (HRG) codes (SB12Z,SB15Z). There are also Outpatient HRG codes for these administration costs (£199 and £212 for first and subsequent chemotherapy administrations respectively). We ran a scenario analysis using the combined Daycase and Reg Day/Night HRG codes and Outpatient HRG codes (section 4.4).

Table 23 Intervention and comparator regimens (CS Table 26)

Technology	Drug	Dose	Days	Cycle length (days)	Stopping rule
Rd	Lenalidomide	25 mg once daily	1 to 21	28	Until progression or unacceptable toxicity
	Dexamethasone	40 mg once daily	1, 8, 15 and 22	28	Until progression or unacceptable toxicity
MPT	Melphalan	0.25 mg/kg	1 to 4	42	12 cycles (72 weeks)
	Prednisone	2 mg/kg	1 to 4	42	12 cycles (72 weeks)
	Thalidomide	200 mg	1 to 42	42	12 cycles (72 weeks)
VMP	Bortezomib	1.3 mg per m^2	1, 4, 8, 11, 22, 25, 29 and 32 (Cycles 1–4) 1, 8, 22 and 29 (Cycles 5–9)	42	9 cycles (54 weeks)
	Melphalan	9 mg per m^2	1 to 4	42	9 cycles (54 weeks)
	Prednisone	60 mg per m^2	1 to 4	42	9 cycles (54 weeks)

The unit costs of the comparator regimens were taken from eMit,[59] where available, or MIMS.[60] The drug costs and dosages are shown in Table 24 (CS Table 35).

A patient access scheme (PAS) has been approved for lenalidomide whereby the cost of the drug is capped at 26 cycles, after which point the company bears the cost and the drug is free to the NHS. The CS proposes an adaptation to the PAS whereby the cost of lenalidomide is capped at [redacted] cycles, after which point the company pays the drug costs. This PAS is conditional on a positive recommendation from NICE for this appraisal. After [redacted] cycles, an administration cost of applying the PAS is included at £22.60 per cycle.

Table 24 First-line drug costs (CS Table 35)

First Line Regimens (Trial data: Rd and MPT)					
Treatment Name	**Drug**	**Dose**	**Unit**	**Pack size**	**List price**
Rd	Lenalidomide	2.5	mg	21	£3,426.00
	Lenalidomide	5.0	mg	21	£3,570.00
	Lenalidomide	10.0	mg	21	£3,780.00
	Lenalidomide	15.0	mg	21	£3,969.00
	Lenalidomide	20.0	mg	21	£4,168.00
	Lenalidomide	25.0	mg	21	£4,368.00
	Dexamethasone	20.0/40.0	mg	50x2	£28.93
MPT	Thalidomide	50.00	mg	50	£298.48
	Melphalan	0.25	mg/kg	25x2	£45.38
	Prednisolone	2.0	mg/kg	56x25	£26.19
VMP	Bortezomib	1.3	mg/m^2	3.5	£762.38
	Melphalan	9	mg/m^2	25x2	£45.38
	Prednisone	60	mg/m^2	56x25	£26.19

In the company's base case, dosing data was taken directly from the MM-020 trial for Rd and MPT. The dosing data included the number of patients on each dosage of each drug at every cycle. These data were combined with the unit drug costs and the number of patients receiving treatment to give a total weighted cost per cycle. In the absence of trial-level dosing for VMP, the company used the proportion of eligible patients on Rd treatment at each 42-day cycle to estimate VMP costs.

The company includes a sensitivity analysis that uses an alternative method of costing using mean relative dose intensity from the MM-020 CSR and trial publication.[22 23] The scenario is described in more detail in section 4.3.10.

The company's economic analysis also includes additional treatments to prevent adverse events. Patients treated with Rd and MPT also take aspirin or enoxaparin sodium to prevent venous thromboembolism, and patients receiving VMP take acyclovir to prevent herpes. Granulocyte-colony stimulating factor (G-CSF) is taken to improve the patients' immune system while taking immunomodulatory drugs, and usage for Rd and MPT were taken from the MM-020 CSR.[23] The costs and doses of these additional treatments are shown in CS Table 36.

The ERG noted a couple of errors relating to the reporting of the drugs costs. The company explained in the answer to clarification question B2 that the weighted costs per model cycle in CS Table 35 is an error in the submission, and should be reported as £[redacted] for lenalidomide, and £30.64 for dexamethasone, as per the model. The pack cost reported for melphalan and prednisolone were incorrect in some cells in the economic model. The company clarified in clarification question B3 the costs should be £45.38 per pack for melphalan (Drug Costs I97), and £26.19 for prednisolone (Drug Costs I97). However, changing these costs does not alter the ICER for Rd versus VMP. The company submitted an economic model with the clarification responses that corrected this.

4.3.7.2 Subsequent treatment costs

Following progression, the majority of patients receive subsequent lines of treatment. The distribution of subsequent treatment is based upon the MM-020 and VISTA trials shown in Table 25 (CS Table 46). The company conducts a scenario analysis removing subsequent thalidomide treatment costs. As we have commented earlier, the company's preferred comparison is Rd versus VMP. As VMP is only recommended in patients intolerant or contraindicated to thalidomide these patients would not receive thalidomide in subsequent treatment lines. The ERG has conducted a scenario analysis where patients initially receiving Rd or VMP do not receive thalidomide in subsequent treatment lines but instead receive other treatments (section 4.4).

Table 25 Proportion of patients on subsequent therapy and total costs (CS Table 46)

1L	Received subsequent therapy	Therapy received			Source	Total costs
	2L	**Bort**	**Thal**	**Len**		
Rd	299	179	36	41	MM-020 CSR[23]	[redacted]
MPT	381	170	25	150	MM-020 CSR[23]	[redacted]
VMP	178	25	71	26	Mateos et al., 2010.[19]	[redacted]
	3L+	**Bort**	**Thal**	**Len**		

Rd	180	99	31	34	MM-020 CSR [23]	[redacted]
MPT	231	133	13	130	MM-020 CSR[23]	[redacted]
VMP	79	21	23	34	Mateos et al., 2010.[19]	[redacted]

Key: 1L, fist line; 2L, second line; 3L, third line;

Subsequent treatments are included in the model by assuming that all patients starting second or third line treatments receive the mean treatment cycles in the trials (Table 26) and these costs are incurred in the first cycle of second or third line treatment. The duration of subsequent treatments is shown in Table 26 (CS Table 45).

Table 26 Post-progression treatment durations (CS Table 45)

Treatment at each line	Source(s) of the data	Mean cycles used in model
Second line		
Lenalidomide-based therapy	MM-009 and MM-010 studies (no multiple prior relapses)	[redacted]
Bortezomib-based therapy	APEX trial	5.0
Thalidomide-based therapy	OPTIMUM trial	7.0
Third line		
Lenalidomide-based therapy	MM-009 and MM-010 studies (no multiple prior relapses)	[redacted]
Bortezomib-based therapy	APEX trial	5.0
Thalidomide-based therapy	OPTIMUM trial	7.0

The duration between first progression and second progression is taken from MM-020 CSR for Rd and MPT,[23] and for VMP is assumed to be the same as for MPT. The model converts this duration into cycle probability of second progression, shown in Table 27 (CS Table 43).

Table 27 Subsequent treatment time inputs (CS Table 43)

	1L fatal progression rate from MM-020	Time from 1st to 2nd progression (months)	Time from 1st to 2nd progression (cycles)	Rate of progression (per cycle)	Cycle probability of 2nd progression
Rd	23.1%	16.9	18.4	0.053	0.052
MPT	25.9%	13.1	14.2	0.068	0.066
VMP	25.9%	13.1	14.2	0.068	0.066

Key: 1L, first line;
Note: If before the 92-week cut-off values from the MM-020 trial as described are used. After this cut-off, the transitions from the MSM matrices are used: progression-free to death/(progression-free to death + progression-free to progressed).

The costs of subsequent treatments are shown in CS Table 44. The company includes the PAS for lenalidomide for its use as second and third line treatment where treatment costs are capped

at 26 cycles for the comparator arms and [redacted] cycles in the intervention arm (based on the proposed PAS adaptation). The ERG includes a scenario analysis where the treatment costs for lenalidomide for second and third line treatment are capped at [redacted] weeks (section 4.4). The cost per cycle for bortezomib in second-line includes a PAS, according to NICE Technology Appraisal TA129.[7] The company assumes a reimbursement per patient of £3,097.31, based upon 6% of patients being eligible for rebate at two cycles and 23% being eligible for rebate at four cycles. The company conducts scenario analyses exploring the impact of different assumptions for the PAS for bortezomib.

4.3.7.3 Health state costs

The health state costs are based on the number of health visits and assessments, including routine laboratory tests and monitoring. The company conducted a survey of seven UK clinicians in 2015, to provide annual rates of laboratory tests and monitoring pattern for patients receiving Rd, MPT and VMP and subsequent lines of therapy. The results of the survey are shown in CS Table 40 for the health care resources used per year. Unit costs for the laboratory tests were obtained from the 2015-16 National Reference Costs,[58] shown in CS Table 42. Costs were also included for platelet and red blood transfusions using resource data from the MM-020 CSR[23] and NICE Technology Appraisal TA228.[6] The health state costs for first and subsequent treatment lines are shown in Table 28 (CS Table 37).

Table 28 Health state costs

Health states	Items	Value (per cycle)		
		Rd	MPT	VMP
Pre-progression	Health visits & assessments	£229	£202	£260
Post-progression	Health visits & assessments	£216	£216	£216

4.3.7.4 Adverse event costs

Adverse event costs were included for treating Grade 3 and 4 AEs that occurred during the treatment phase in more than 5% of patients. Frequency of adverse events were taken from the MM-020 trial for Rd and MPT and from the VISTA trial[20] for VMP and are shown in CS Table 38. Cost of treating the adverse events were taken from National Reference Costs[58] and are shown in CS Table 39.

In summary, the ERG considers that that the approach taken by the company for estimating health care resources and costs is reasonable. There is some uncertainty around the costing of

subsequent treatment costs. The company proposes that the most relevant comparison for this appraisal is between Rd and VMP, where VMP is currently only recommended in patients who are ineligible or intolerant to thalidomide. However, the trials from which the data used for costing subsequent treatment is based include patients who receive thalidomide in subsequent lines of treatment.

4.3.8 Model validation

The ERG checked the economic model for transparency and validity, in line with the recommendations developed by a task force of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM)[61] for model quality assurance.

4.3.8.1 Model transparency

The model structure, parameter values and their sources, data identification methods and the assumptions used in the model were clearly described in the CS. The model was technically transparent and the visual basic code used within the model was accessible. The CS and the model described the analyses clearly and provided adequate information to assess the model.

4.3.8.2 Model validation

The CS stated that the programming of the economic model was validated by both internal and external modellers. All the model formulae and labels were reviewed by a programmer who was not involved in developing the model. In addition, the company conducted extreme value tests to examine if the model produced the expected results. Finally, an academic health economist validated and critiqued the modelling strategy and methodology of the company model.

The ERG checked the model for internal and external validity. A discussion is presented below of the step-by-step approach used for this purpose.

Face validity

The CS presented an extensive review of the existing literature in multiple myeloma, including NICE appraisals to inform their modelling approaches. The company's model structure is widely used for representing patients' transition in oncology. A systematic search was also conducted to identify utility studies to inform the quality of life parameters. Further, the CS also presented the resource use questionnaire in CS Appendix I which the company used as a validation tool for the resource use data (obtained via physician interviews) associated with the treatment of elderly patients who are newly diagnosed with multiple myeloma and ineligible for transplant in

the UK. The CS presented an example of the extreme value test conducted (i.e. setting all AE costs to £0), but they did not explicitly document the steps taken to validate the model calculations and the data sources. Therefore, the ERG is unable to comment on these. Further, no information was presented to ascertain if the model assumptions were validated by clinicians or experts.

Internal validity

The ERG adopted two steps for internal validity: checking the individual equations within the model; and verifying their accurate implementation in code. First, the ERG checked individual equations for their mathematical correctness focussing primarily on the equations defining survival functions, patient transition in different health states, costs, QALYs and overall results. Secondly, the visual basic programming code within the model was checked and appeared to be correct. Thirdly, the ERG checked for consistency of the parameters reported in the CS and those utilised within the model as discussed earlier in section 4.3.7.1. Briefly, we identified two inconsistencies in values reported in the CS and those used in the model relating to the weighted drug costs per model cycle and pack cost of melphalan and prednisolone. The company clarified that there was a reporting error of the value used for the weighted drug cost per model cycle in the CS and that the model used the appropriate value, indicating that there is no change in the base case model results (Clarification response to Question B2). With respect to the pack cost of melphalan and prednisolone, the company acknowledged that the model used incorrect values which were corrected as part of the clarification response (Clarification response to Question B3). However, this correction did not influence the base case results. Finally, the ERG conducted a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed. The observed outcomes from these tests matched the expected model outcomes.

The ERG identified a minor calculation error in the model, with respect to the estimation of terminal care costs in cell F89:I89 within '*Sheet!Results'* of the company's model. Correcting this error did not have any impact on the overall base case model results.

External validity

As part of the external validity checks, the company compared the predicted clinical outcomes of time on treatment, PFS and OS against the observed values in the MM-020 and VISTA trials for the treatment options. These are summarised in Table 29.

Table 29 Comparison of the predicted clinical model outcomes against the observed outcomes

Time to Treatment Failure (median)

Arm	Modelled values	Observed values	
		MM-020 trial	VISTA trial
Rd	[redacted]	20.05	--
VMP	[redacted]	--	--
MPT	[redacted]	16.78	--

Source: CS Appendix J Table 42

PFS months (median)

Arm	Modelled values	Observed values	
		MM-020 trial	VISTA trial
Rd	[redacted]	26.0	--
VMP	[redacted]	--	24.0
MPT	[redacted]	21.9	--

Source: CS Table 53

Four year OS (%) and median OS months

Arm	Modelled values		Observed values		
	4 year (%)	Median (months)	MM-020 trial		VISTA trial
			4 year (%)	Median (months)	Median (months)
Rd	[redacted]	[redacted]	58.99	59.1	--
VMP	[redacted]	[redacted]	--	--	56.4
MPT	[redacted]	[redacted]	51.67	49.1	--

Source: CS Table 54

In general, the modelled values appeared comparable with the observed values, except for the modelled median OS for VMP ([redacted] months) which was shorter than the observed value in the VISTA trial (56.4 months).[20] The CS stated that a potential reason for this difference in values could be due to using the MPT arm of the MM-020 trial as the reference for the HR for OS for VMP. Further, the CS cited that the patient population in the VISTA trial was healthier compared to those in MM-020 trial. The ERG considers the rationale given by the company may explain the discrepancy. The ERG also notes that the HR of the VMP OS had the most influence in the base case cost-effectiveness results and there is considerable uncertainty attached to this parameter. To address this, we conducted a scenario analysis (presented in section 4.4) by using the assumption of similar effectiveness for the OS HR for MPT vs VMP to replicate the clinical outcomes in NICE TA228.[6 48]

Cross validation

Cross validation checks involve comparing different mathematical models addressing the same decision problem. The company compared the findings of this appraisal with those reported in the multiple technology appraisal of bortezomib and thalidomide used in NICE TA228[6 48] and the economic evaluation by Usmani et al[51] as shown in Table 30.

Table 30 Comparison of the model findings with the existing literature

Parameter	Predicted model	NICE TA228	Usmani et al.
Incremental LYs gained for MPT vs VMP	[redacted]	0.02	--
Incremental pre-progression LYs for Rd vs VMP	[redacted]	--	1.30
Incremental post-progression LYs for Rd vs VMP	[redacted]	--	1.94

Key: LY= life years

The CS reported that the difference in the values of incremental life years for MPT vs VMP obtained in this appraisal and that reported in NICE TA228 could be due to a different reference treatment for the HR (the HR values in TA228 were not available). The ERG also notes that the company has used an updated data cut of the VISTA trial to that used in TA228 which produces a different HR for VMP vs. MPT.

The CS reports that incremental pre-progression life years for Rd vs VMP were comparable between this appraisal and that reported by Usmani et al.[51] ([redacted] vs 1.30 respectively). However, there was a substantial difference in incremental post-progression life years ([redacted] vs 1.94 respectively). The CS noted that this difference in values could possibly be due to differences in extrapolation methods, the MM-020 trial data cut, discount rates for outcomes and studies included in the NMA between the two studies.

4.3.9 Cost effectiveness results

The CS presents base case results in terms of total costs, life years gained, QALYs and incremental cost per QALY. Two sets of base case results were presented: Rd versus MPT and Rd versus VMP (in patients who are intolerant or contraindicated to thalidomide). The base case results are obtained based on the proposed PAS adaption wherein the cost of lenalidomide is capped at [redacted] cycles (CS Appendix P presents results with the existing approved PAS cap at 26 cycles).

The results of the incremental analyses of Rd versus MPT and VMP are reproduced from CS Table 49 and 50 in Table 31 and Table 32 below respectively.

Table 31 Results of the base case results for Rd versus MPT

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (per QALY)
MPT	£[redacted]	[redacted]			
Rd	£[redacted]	[redacted]	£[redacted]	[redacted]	£[redacted]

Table 32 Results of the base case results for Rd versus VMP

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (per QALY)
VMP	£[redacted]	[redacted]			
Rd	£[redacted]	[redacted]	£[redacted]	[redacted]	£[redacted]

The above results indicated that whilst Rd did not provide value for money within the willingness-to-pay threshold of £30,000 when compared against MPT, it provided a cost-effective option when compared against VMP for the patients who are unable to tolerate or have contraindications to thalidomide.

4.3.10 Assessment of uncertainty

The company performed a range of deterministic sensitivity-, probabilistic sensitivity-, and scenario analyses to assess methodological, structural as well as parameter uncertainties. They presented the results of these analyses for the comparison of Rd versus VMP only.

Deterministic sensitivity analysis

The company conducted deterministic sensitivity analyses (DSA) on a number of key parameters as listed below in Table 33. Where information was available, the parameters were varied by setting lower and upper bound to ±1.96*standard error (SE) of the mean values or varied using the confidence intervals. Where such information was unavailable, the upper and lower bounds were varied by ±15% of the base case value.

The ERG were unable to ascertain the range used for lower and upper bounds for two parameters: treatment and time coefficients/interactions for utility calculations and time from first to second progression (months). For the remaining parameters, the ranges for variation were reasonable.

Table 33 Parameters included for DSA

Parameters	Range used in DSA
Discount rates	0%-6%
HR for VMP versus MPT PFS	95% credible interval
HR for VMP versus MPT OS	95% credible interval
Kaplan-Meier uncertainty i. PFS KM uncertainty HR Rd ii. PFS KM uncertainty HR MPT iii. OS KM uncertainty HR Rd iv. OS KM uncertainty HR MPT v. TOT KM uncertainty HR Rd vi. TOT KM uncertainty HR MPT	±15% of the base case value
AE rates	95% confidence interval
Baseline utility	±15% of the base case value
Treatment and time coefficients/interactions for utility calculations	Unclear
Resource use frequency	±15% of the base case value
% of patients completing at most two and four cycles of bortezomib treatment	95% confidence interval
% of patients on prophylactic aspirin	±15% of the base case value
% of patients requiring G-CSF annually	95% confidence interval
Subsequent treatment relative dose intensity	95% confidence interval
AE costs	±15% of the base case value
First line fatal progression probability (pre-cut off)	95% confidence interval
Time from first to second progression (months)	Unclear
Duration of subsequent treatment	±15% of the base case value

Key: TOT – time on treatment; G-CSF = Granulocyte-colony stimulating factor

The company produced tornado plots with parameters shown in decreasing order of ICER sensitivity. The ERG was able to derive similar results from running the DSA. The tornado diagram, reproduced from CS Figure 26, is presented below in Figure 16.

Figure 16 Results of DSA for Rd versus VMP (CS Figure 26)

The results of the DSA indicated that whilst the model was relatively insensitive to change in the majority of the parameters, the OS HR for VMP had the largest impact on the ICER ranging from £[redacted] per QALY for the upper credible interval value and increasing up to £[redacted] per QALY for the lower credible interval value. This indicates a considerable amount of uncertainty associated with the prediction of OS HR for VMP. Other parameters including discount rates, parameters for TTF and utilities also influenced the base case results, but to a lesser extent.

Probabilistic sensitivity analysis

Parameter uncertainty was assessed by conducting a probabilistic sensitivity analyses (PSA) on the company's base case. The parameters, together with the chosen distribution, are reproduced from CS Table 47 in Table 34 below.

The CS presented the results of the PSA for 1000 simulations. The ERG re-ran the analyses which took approximately seven minutes to run. We considered the distributions assigned to the parameters to be appropriate.

Table 34 List of parameters and associated distributions included in the PSA (CS Table 47)

Variable	Measurement of uncertainty and distribution: CI (distribution)
HR for VMP versus MPT PFS	CODA samples
HR for VMP versus MPT OS	CODA samples
MSM transition probabilities	Bootstrapped samples
KM uncertainty	Normal distribution with SE of 0.13 (calibrated)
AE rates	Beta distribution (MM-020 and VISTA)
Baseline utility	Beta distribution (SE from MM-020 patient-level data analysis)
Treatment and time coefficients/interactions for utility calculations	Multivariate normal distribution (variance/covariance from PLD analysis)
Resource use frequency	Normal distribution (SE 15% of mean)
% of patients completing at most two and four cycles of bortezomib treatment	Beta distribution (Lee et al. 2008)
% of patients on prophylactic aspirin	Beta distribution (SE 15% of mean)
% of patients requiring G-CSF annually	Beta distribution (MM-020)
Subsequent treatment relative dose intensity	Normal distribution (SE 15% of mean)
AE costs	Normal distribution (SE 15% of mean)
First line fatal progression probability (pre-cut off)*	Beta distribution (MM-020)
Time from first to second progression (months)	Normal distribution (MM-020)
Duration of subsequent treatment	Normal distribution (SE 15% of mean)

Key: CODA = convergence diagnosis and output analysis; G-CSF = Granulocyte-colony stimulating factor

*uncertainty in fatal progression post cut-off is captured in the MSM bootstraps.

The results of the PSA were tabulated in CS Table 51, reproduced in Table 35 below. The point estimates from the average PSA results for Rd versus VMP were close to the results obtained from the deterministic analysis as summarized in Table 32.

Table 35 Results from the PSA for Rd versus VMP

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (per QALY)
VMP	£[redacted]	[redacted]			
Rd	£[redacted]	[redacted]	£[redacted]	[redacted]	£[redacted]

At a willingness-to-pay threshold of £20,000 per QALY, the probability of Rd being cost-effective is [redacted] compared to VMP. The probability increases to [redacted] when the threshold is £30,000 per QALY. The cost effectiveness acceptability curves, obtained from the company's model are presented in Figure 17.

Figure 17 Cost-effectiveness acceptability curve (reproduced from CS Figure 25)

Scenario analyses

The company conducted a total of 17 scenario analyses to assess structural and methodological uncertainties of their base case assumptions. These analyses, along with their justifications and the results obtained are presented in Table 36 from CS Table 52.

Table 36 Summary of the scenario analyses (CS Table 52)

Scenario and cross reference	Brief rationale	ICER (vs VMP)
Base case		£[redacted]
Time horizon of 15 years	To observe the impact of the ICER on the model time horizon. This is impact minimal.	£[redacted]
Time horizon of 35 years		£[redacted]
Equal OS and subsequent therapy for VMP and MPT	To observe the impact of equal efficacy of VMP to MPT, which would be reflected with increased subsequent Rd use than reported in VISTA	Rd Dominates

Equal PPS for Rd and MPT	To observe impact of assuming no post-progression survival benefit for the Rd arm	£[redacted]
Time-varying HRs for VMP vs MPT	To observe the impact of relaxing the proportional hazards assumption	£[redacted]
Time-varying HRs for VMP and Rd vs MPT		£[redacted]
Use TTF:PFS to extrapolate Rd and MPT duration of treatment	An alternative method of estimated costs to parametric modelling of TTF from patient-level data from MM-020	£[redacted]
Use Rd TTF:PFS for VMP duration of treatment	In the absence of data, this scenario tests the impact of assuming Rd treatment discontinuation is applicable to the VMP arm	£[redacted]
Assume VMP duration of treatment from NICE TA228	In the absence of data, this scenario tests the impact of assuming previous technology appraisal costings	£[redacted]
Use Relative dose intensity for drug costs	An alternative method to estimate drugs costs to the trial-based dosing	£[redacted]
VMP G-CSF equivalent to MPT	In the absence of data, this scenario estimates the impact of equal G-CSF use between VMP and MPT rather than Rd	£[redacted]
Assume 100% VMP patients receive full rebate for bortezomib if achieving less than a partial response by the cut-off duration	Explores the impact of assuming all patients receive the reimbursement, rather than 75%	£[redacted]
Exclude bortezomib PAS	To observe the impact on the ICER of the bortezomib PAS (minimal)	£[redacted]
Remove subsequent thalidomide costs	To observe the impact on the ICER of subsequent thalidomide use given the subgroup explored is patients who are unable to tolerate, or have contraindications to thalidomide	£[redacted]
Remove all subsequent treatment costs	To observe the impact on the ICER of subsequent treatment use	£[redacted]
Include subsequent-treatment disutilities	An alternative method of calculating post-progression utility	£[redacted]
Remove treatment coefficient and interaction terms for utility calculations	To observe the impact on the ICER of the treatment in utility calculations	£[redacted]

For the scenarios related to treatment effectiveness the company performed a scenario analysis relating to OS where equal efficacy and subsequent therapy use was assumed for VMP and MPT, which resulted in Rd dominating VMP. In another scenario, the company removed the treatment effect of Rd in post progression by assuming equal PPS for Rd and MPT. This had insignificant impact on the base case ICER. The assumption of proportional hazards was relaxed in two scenarios where fractional polynomials were used to estimate the PFS and OS HR for VMP and for VMP and Rd to MPT. The parameters used in these scenarios are shown in CS Table 19. These assumptions reduced the ICERs to £[redacted] per QALY and £[redacted] per QALY respectively. In another scenario, they applied the treatment discontinuation of Rd to the VMP arm which marginally increased the ICER to £[redacted] per QALY.

With respect to costings, the company conducted scenarios where they assume: patients receive all 9 doses of VMP; use an alternative costing method with relative dose intensity for Rd, MPT and VMP drug costs; equal usage of G-CSF between VMP and MPT; all patients receiving VMP receive a full rebate, excluding the PAS associated with bortezomib, removing all subsequent thalidomide costs and all subsequent treatment costs. All these scenarios had minimal impact on the base case ICER. Finally, for utilities two scenarios were included: one used an alternative approach of estimating post-progression utility by including subsequent treatment disutilities and the other scenario excluded treatment coefficient and interaction terms for utility calculations. None of these scenarios influenced the base case ICER of Rd vs VMP significantly.

The ERG re-ran all the above scenarios (presented in Table 36) and replicated the results reported by the company. The ICERs ranged from Rd dominating VMP (scenario: VMP HR for OS and subsequent therapy proportions are set equal to MPT) to £[redacted] per QALY (scenario: using the ratio of TTF to PFS from the Rd and MPT arms of the MM-020 trial, and applying to PFS to estimate DoT). Overall, we view that the company has appropriately tested a range of their key model assumptions relating to model time horizon, treatment effectiveness, resource use and costing, and utility estimation in their scenario analyses. The results, in general, indicate that alternative scenarios provided broadly similar results to the base case.

4.4 Additional work undertaken by the ERG

This section discusses the ERG's further exploration of the issues and uncertainties raised in their review and critique of the CS. In particular, the ERG considered the CS base case to be limited with regard to the assumptions relating to time to treatment failure for VMP, HRQoL estimation, subsequent treatments and administration costs for VMP.

A summary of the analyses conducted by the ERG are outlined below in Table 37, along with their justifications and how these analyses changed parameters from the CS base case. These analyses culminate in the ERG base case (ERG preferred scenario), which we believe to be the most representative and appropriate analysis for the cost-effectiveness of Rd versus VMP for treating patients with multiple myeloma. The results of the ERG additional analyses are presented in the following sub-sections.

Table 37 Additional analyses conducted by the ERG

ERG Scenario analysis	Analysis description	Company's base case assumption	ERG assumption	Justification
1	TTF	TTF curve for VMP is assumed to equal PFS up to the maximum treatment duration	TTF for VMP is equal to MPT	Current approach for VMP inconsistent with that taken for Rd and MPT. PFS for MPT and VMP is similar (HR=1)
		TTF parametric curve for MPT is assigned an exponential distribution	TTF parametric curve for MPT is assigned a Weibull distribution	NICE DSU TSD guidelines advocates the use of same parametric curve for both the treatment arms
2	Treatment effectiveness	OS HR for VMP vs MPT =1.11	OS HR for VMP vs MPT =1.0	To make the assumption of no difference in OS for VMP vs MPT as in NICE TA228[48]
3	HRQoL estimation	VMP is administered in 42 day treatment cycle whereas the utility is assigned to 28 day cycle	Adjusted the cycle length for VMP	Incorrect cycle duration for VMP with regard to utility: VMP is administered in 42 day treatment cycles, whereas the utility has been assigned to 28 day cycles
		Assumes continued HRQoL benefit for Rd after end of MPT treatment for PFS	Assumes no difference in HRQoL Rd after the end of MPT treatment for PFS	Patients treated with Rd continue to have higher utility than those treated with MPT and VMP once their treatment is finished. We consider a better assumption would be to have equal utility values in all the three arms after MPT and VMP treatment has finished, based on EQ-5D data presented by the company
4	(i) Subsequent treatment costs – remove thalidomide	Inclusion of thalidomide as a subsequent treatment for VMP and Rd first line treated patients	Exclusion of thalidomide as a subsequent treatment for VMP and Rd first line treated patients	The comparison of Rd with VMP is only for patients who are intolerant to or contra-indicated to thalidomide

	(ii) Subsequent treatment costs - remove thalidomide and lenalidomide	Inclusion of thalidomide and lenalidomide as a subsequent treatment for VMP and Rd first line treated patients	Exclusion of thalidomide as a subsequent treatment for VMP and Rd patients, and exclude Rd as subsequent treatment in Rd first line treated patients	Patients who progress on first line Rd would not be given Rd in a subsequent line.
	(iii) Rd PAS in subsequent treatment lines	Rd PAS cap restricted to 26 cycles in comparator arm	Adapted Rd PAS cap restricted to [redacted] cycles in comparator arm	NICE request: to reflect cost to the NHS if new PAS adaptation is approved.
5	VMP administration costs	First administration: £253, Subsequent administration: £361	First administration: £236.19, Subsequent administration: £328.10	Using outpatient and Day case HRG codes for administration
ERG base case	Version 1: scenarios 1, 3, and 5	As above	As above	Reflects the ERG's preferred most plausible assumptions
	Version 2 (exploratory): Scenarios 1, 3, 4 and 5	As above	In addition to scenario 1, 3 and 5, this ERG scenario also explores the impact of Rd patients not receiving thalidomide as second line or third line treatment.	To reflect the impact of excluding thalidomide subsequent treatment costs in the ERG base case.

Key: DSU = Decision Support Unit. TSD = technical support document

4.4.1.1 ERG scenario 1: Assumption on time to treatment failure

As stated in section 4.3.5.3, the ERG has concerns relating to the company's assumption that TTF curve for VMP equals to PFS up to the maximum treatment duration. We consider this is inconsistent with the approach taken for Rd and MPT. Further, the company used different parametric curves for Rd and MPT which is inconsistent with the NICE Decision Support Unit Technical Support Document guidelines.[55] Therefore, to address these issues, we ran an analysis wherein the TTF curve for VMP is assumed to be equal to that of MPT, and TTF for Rd and MPT are both extrapolated using the Weibull distribution. The Weibull was chosen in preference to the exponential as this provided the better visual fit for both Rd and MPT. The result of this analysis (shown below in Table 38) increases the ICER by approximately £[redacted] to £[redacted] per QALY compared with the base case ICER.

Table 38 ERG Scenario 1 cost-effectiveness results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
VMP	£[redacted]	[redacted]			
Rd	£[redacted]	[redacted]	£[redacted]	[redacted]	£ [redacted]

4.4.1.2 ERG scenario 2: Treatment effectiveness

The ERG notes that the estimate of the HR for VMP versus MPT for OS in the NMA has a wide credible interval (HR 1.11, 95% CrI: 0.82, 1.50). This indicates high uncertainty, and also that that the difference in OS between VMP and MPT is not statistically significantly different. Further we note that in NICE TA228[6 48] the clinical outcomes for VMP and MPT were similar. We ran a scenario analysis assuming no difference between VMP and MPT for OS, i.e. HR of 1. This assumption resulted in an ICER of £[redacted] per QALY, which is slightly higher than the company's base case ICER (shown below in Table 39).

Table 39 ERG scenario 2 Cost effectiveness results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
VMP	£[redacted]	[redacted]			
Rd	£[redacted]	[redacted]	£[redacted]	[redacted]	£ [redacted]

4.4.1.3 ERG scenario 3: HRQoL estimation

i. Adjusting the cycle length for the VMP HRQoL estimation

In their base case analysis, the company did not adjust for the cycle length for VMP. Like Rd and MPT, the utilities were estimated based on a cycle length of 28 days whereas VMP is administered for 42 day treatment cycle. Using the appropriate VMP cycle length gave an ICER of £[redacted] per QALY which is slightly lower than the company's base case ICER of £[redacted] per QALY (Table 40). This decrease in the ICER is driven by a small decrease in total QALYs for the VMP arm compared to the total QALYs for this arm in the company's base case.

Table 40: ERG Scenario 3(i) cost-effectiveness results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
VMP	£[redacted]	[redacted]			
Rd	£[redacted]	[redacted]	£[redacted]	[redacted]	£ [redacted]

ii. No utility effect of Rd after end of MPT treatment

As outlined in section 4.3.6, in the company's base case, patients in the Rd arm continue to experience higher utility values compared to those in the MPT and VMP arms when their treatment stops. Expert clinical advice to the ERG is that continued Rd treatment would have a utility benefit, as many patients continue to experience residual painful and debilitating neuropathy that sometimes gets worse on stopping treatment, possibly due to the cessation of corticosteroids. However, the ERG notes that there are no data beyond 18 months treatment available from the MM-020 trial to assess the impact of continued treatment on HRQoL. Furthermore, the MPT utility at the final assessment time point (18 months) was slightly higher than the Rd utility (though the difference was not statistically significant). The overall increase in utility (i.e. over the 18 months) was higher for Rd compared to MPT (but again, a non-statistically significant difference) (see section 3.3.6). We therefore consider that there is uncertainty in the difference in utility between Rd and MPT and it would therefore be appropriate to assume that all patients experience similar utility values after the comparator treatments have finished. Therefore, in this scenario, we assume that there is no utility effect for Rd after the end of MPT and VMP treatment which is after 12 cycles for patients. As can be seen in Table 41, this change had a minimal impact on the company's base case ICER.

Table 41 ERG scenario 3(ii) cost effectiveness results.

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
VMP	£[redacted]	[redacted]			
Rd	£[redacted]	[redacted]	£[redacted]	[redacted]	£ [redacted]

4.4.1.4 ERG scenario 4: Subsequent treatment costs

i. **Exclusion of thalidomide from subsequent costs for Rd and VMP patients**

The scope of this NICE appraisal states that the comparison of lenalidomide with bortezomib should only be made for patients intolerant to or contraindicated to thalidomide. However, in the company's economic model thalidomide is included as a subsequent line treatment (CS Table 46). To assess the impact on the cost-effectiveness of Rd vs VMP when patients in these two arms do not receive thalidomide as a subsequent treatment in second and third line treatment, we ran two separate analyses in which we adjusted the number of patients receiving subsequent line treatments, such that none received thalidomide.

In this scenario we assume that Rd and VMP patients do not receive thalidomide as second and third line treatment but can receive bortezomib or lenalidomide (Table 42). The associated cost-effectiveness results are presented in Table 43. The ICER decreases substantially from £[redacted] to [redacted] per QALY favouring Rd over VMP at a willingness-to-pay threshold of £30,000 per QALY.

Table 42 Patient combination for subsequent treatments with Rd and VMP patients not receiving thalidomide in second line and third line

Received second line treatment				
First line treatment	**Population (N)**	**Bortezomib**	**Thalidomide**	**Lenalidomide**
Rd	299	208	0	48
MPT	381	170	25	150
VMP	178	60	0	62
Received third line treatment				
First line treatment	**Population (N)**	**Bortezomib**	**Thalidomide**	**Lenalidomide**
Rd	180	122	0	42
MPT	231	133	13	130
VMP	79	30	0	48

NB. The number of patients receiving subsequent line bortezomib, thalidomide or lenalidomide does not sum to the total number who received subsequent line treatments as some patients received other regimens (not defined in the CS).

Table 43 ERG Scenario 4.i Cost effectiveness results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
VMP	£[redacted]	[redacted]			
Rd	£[redacted]	[redacted]	£[redacted]	[redacted]	£ [redacted]

ii. **Exclusion of thalidomide from subsequent costs for Rd and VMP patients, and exclusion of lenalidomide from subsequent costs for Rd**

In this scenario, we also assume that patients receiving Rd would not receive Rd again as a subsequent treatment. This is because expert advice to the ERG is that patients who progress on continuous Rd treatment would be unlikely to receive it in a subsequent line, as they have effectively become resistant to it. All Rd patients therefore receive bortezomib in second or third line treatment. Patients in the VMP arm are assumed to receive bortezomib and lenalidomide as subsequent treatments (as in scenario 4 i). The patient combination for this scenario is shown in Table 44 and the associated cost-effectiveness results are presented in Table 45. As can be seen, this scenario further reduces the ICER for Rd vs VMP to £[redacted] per QALY.

Table 44 Patient combination for subsequent treatments in Rd arm not receiving thalidomide and lenalidomide and those in the VMP arm not receiving thalidomide in second line and third line

Received second line treatment				
Treatments	**Population (N)**	**Bortezomib**	**Thalidomide**	**Lenalidomide**
Rd	299	256	0	0
MPT	381	170	25	150
VMP	178	60	0	62
Received third line treatment				
Treatments	**Population (N)**	**Bortezomib**	**Thalidomide**	**Lenalidomide**
Rd	180	164	0	0
MPT	231	133	13	130
VMP	79	30	0	48

NB. The number of patients receiving subsequent line bortezomib, thalidomide or lenalidomide does not sum to the total number who received subsequent line treatments as some patients received other regimens (not defined in the CS).

Table 45 ERG scenario 4.ii: Cost effectiveness results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
VMP	£				
Rd	£		£		£

Changing the combination of patients receiving subsequent treatments leads to a substantial reduction of the ICER for Rd vs VMP. As MPT is cheaper than Rd and VMP, there is an increase in the total costs for patients initially treated with Rd and VMP. The increase in the costs for those treated with VMP is greater than for those treated with Rd (as a larger proportion of patients switch from MPT). The incremental costs of Rd compared to VMP are therefore lower.

iii. New PAS

As discussed in section 4.3.7, in the base case the company caps the cost of lenalidomide at 26 cycles for second and third line treatments in the comparator arms. The ERG ran a scenario analysis assuming the cost of lenalidomide is restricted to cycles when used as a subsequent treatment in the comparator arms, to be consistent with the cycle PAS adaptation applied to the subsequent treatment lines for the intervention arm. Whilst adopting the adapted cycle PAS cap marginally increases the base case ICER (as presented in Table 46), the overall effect is marginal when compared with the company's base case results.

Table 46 ERG Scenario 4 (iii) cost effectiveness results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
VMP	£				
Rd	£		£		£

4.4.1.5 ERG scenario 5: VMP administration costs

The ERG suggests a different cost for VMP administration based on using the combined HRG codes for Daycase and Outpatients, rather than just the Daycase HRG codes, stated in section 4.3.7.1. Using the combined outpatient and Daycase HRG costs of £236.19 for first administration and £328.10 for the subsequent administrations marginally increases the ICER to £ as shown in Table 47.

Table 47 ERG Scenario 5 cost effectiveness results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
VMP	£[redacted]	[redacted]			
Rd	£[redacted]	[redacted]	£[redacted]	[redacted]	£ [redacted]

4.4.1.6 ERG base case

We present two versions of the ERG base case as outlined below:

- Version 1: Combines ERG scenarios 1, 3 and 5
- Version 2: Combines ERG scenarios 1, 3, 4 and 5

Version 1

The ERG base case combines ERG scenarios 1, 3 and 5, i.e. changes to TTF, HRQoL and VMP administration costs. We consider that this scenario represents the most plausible model assumptions. The ERG base case cost effectiveness results (presented in Table 48) show an ICER of £[redacted] per QALY for Rd vs VMP which is an increase of £[redacted] from the company's base case ICER of £[redacted] per QALY.

Table 48: ERG base case cost-effectiveness results (Version 1)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
VMP	£[redacted]	[redacted]			
Rd	£[redacted]	[redacted]	£[redacted]	[redacted]	£[redacted]

The results of the PSA are presented in Table 49 below. At a willingness-to-pay threshold of £20,000 per QALY, the probability of Rd being cost-effective is [redacted] compared to VMP. The probability increases to [redacted] when the threshold is £30,000 per QALY. The cost effectiveness acceptability curves are presented in Figure 18.

Table 49 ERG Base case Results from the PSA for Rd versus VMP (Version 1)

Treatments	Incremental costs (mean)	Incremental QALYs (mean)	ICER (per QALY) (mean)
Rd vs VMP	£[redacted]	[redacted]	£[redacted]

Figure 18 Cost effectiveness acceptability curves for the ERG Base case (Version 1)

Version 2 (exploratory)

This version of the ERG base case combines ERG scenario 4.ii. for changes to subsequent treatment costs with ERG scenarios 1, 3 and 5. In scenario 4 ii, patients treated initially with Rd and VMP do not receive thalidomide as a subsequent treatment and those receiving Rd as first line would not receive Rd as a subsequent treatment (Table 44). Scenario 4 was not included in version 1 of our base case analysis because the subsequent treatments we have modelled, although reflective of clinical practice, are different to the subsequent treatments used in the MM-020 trial and there may have been changes to OS if alternative subsequent treatments had been used, which we are not able to quantify. For this reason we consider version 2 of our base case to be exploratory.

The cost effectiveness results of this version of the ERG base case (Table 50) show an ICER of £[redacted] per QALY for Rd vs VMP which is a decrease of £[redacted] from the results obtained from the version 1 of the ERG base case of £[redacted] per QALY and a decrease of £[redacted] from the company's base case ICER of £[redacted] per QALY.

Table 50 ERG base case cost-effectiveness results (Version 2)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
VMP	£[redacted]	[redacted]			
Rd	£[redacted]	[redacted]	£[redacted]	[redacted]	£[redacted]

The results of the PSA are presented in Table 51 below. At a willingness-to-pay threshold of £20,000 per QALY, the probability of Rd being cost-effective is [redacted] compared to VMP. The probability increases to [redacted] when the threshold is £30,000 per QALY. The cost effectiveness acceptability curves are presented in Figure 19.

Table 51 ERG base case Results from the PSA for Rd versus VMP (Version 2)

Treatments	Incremental costs (mean)	Incremental QALYs (mean)	ICER (per QALY) (mean)
Rd vs VMP	£[redacted]	[redacted]	£[redacted]

[redacted]

Figure 19 Cost effectiveness acceptability curves for the ERG base case (Version 2)

4.5 Conclusions of cost effectiveness

The company used a model structure commonly used for economic models of cancer treatment with health states for progression-free survival, progression and death. The model chosen was a hybrid structure that consisted of partitioned survival analysis for the first 92 weeks and a

Markov modelling structure thereafter. Although it has been more common to use partitioned survival analysis for the full time horizon in previous cancer technology appraisals, the ERG considers that the approach taken by the company is appropriate in this instance as we consider there is a good fit between the economic model and the Kaplan-Meier data. The company used methods for the economic evaluation that are consistent with the NICE methodological guidelines. The company compares Rd with MPT using the company's MM-020 trial and compares Rd with VMP using an NMA.

The population, intervention and comparators accord with those listed in the NICE scope. However, the company's preferred comparison of Rd versus VMP is only applicable to patients who are intolerant or contra-indicated to thalidomide, whereas the MM-020 trial – which compared Rd with MPT - was not conducted in this population. Expert clinical advice to the ERG is that this would not influence the generalisability of clinical effectiveness outcomes from this trial.

The ERG considers that the company's approach to estimating HRQoL used in the economic model follows the NICE reference case: EQ-5D-3L values have been used for the model health states. The company has used utility values for MPT and Rd from the MM-020 trial and so the values used are directly related to the population considered. However, there is uncertainty around the utility values for progressed disease as these were based only upon observations taken on the first outpatient visit post-progression. Also some uncertainty around the utility values used for VMP as these have been taken from a mapping from EORTC QLQ Q30 to EQ-5D. The approach taken by the company for estimating health care resources and costs is reasonable. There is some uncertainty around the costing of subsequent treatment costs.

The model results are most sensitive to changes in the HR for VMP compared to MPT and assumptions regarding the proportions of patients taking subsequent therapy for patients who are ineligible for thalidomide. As noted above, the population included in the analysis for Rd vs. VMP differs from that used in MM-020 trial as the analysis is for patients not eligible for thalidomide whilst the trial includes patients treated with thalidomide. The impact of excluding thalidomide from subsequent therapy for patients initially treated with Rd or VMP is more favourable to Rd (i.e. the ICER reduces) because there are higher additional costs for VMP than for Rd (more VMP patients receive subsequent line bortezomib-based therapy than the cheaper thalidomide-based therapy). However, it is unclear how the clinical effectiveness outcomes

would be affected by excluding thalidomide as subsequent treatment. Potentially the clinical benefit of Rd versus VMP would be reduced in this group if patients initially treated with VMP had Rd second-line rather than MPT, and patients initially treated with Rd had VMP second-line rather than MPT.

The ERG notes limitations in the company's approach with regard to treatment failure for VMP, HRQoL estimation and administration costs for VMP. The ERG conducted analyses with regard to these issues but, in general, these analyses had only a small impact on the ICER of Rd compared to VMP.

5 End of life

The CS does not consider that lenalidomide meets all of NICE's end-of-life criteria (CS Table B.2.13.5). The ERG agrees with this.

6 Innovation

The CS states that the innovative nature of lenalidomide is based on its mechanism of action and toxicity profile. Lenalidomide is more potent than thalidomide in terms of its anti-proliferative activity, anti-inflammatory properties and ability to stimulate Th1 cytokines, T-cells and natural killer cells (CS section B.2.12). It is possible for lenalidomide to be used continuously to suppress residual disease and extend the period of first remission, unlike the other treatments which are given for a fixed period.

The CS notes that lenalidomide can also be given in a two-drug combination that does not include melphalan, thus making treatment more tolerable to older frail patients. Expert clinical advice to the ERG is that melphalan can be hard for some elderly patients to tolerate.

The CS highlights that in comparison to MPT and current therapies, Rd can be given orally, providing an alternative treatment to current intravenous and subcutaneous therapies. The combination of lenalidomide and low-dose dexamethasone can be self-administered by patients at home, which is proposed to be more convenient, easier and less distressing for patients than use of either intravenous or injectable combinations (e.g. VMP), particularly for elderly and frail individuals as well as those who do not live near to a hospital. The CS claims that use of an oral

agent provides patients with a greater sense of control over their disease and less interruption of their daily (including work) lives compared to intravenous and subcutaneous treatments. The ERG agrees that this is a reasonable suggestion.

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The clinical effectiveness evidence for lenalidomide comes from the phase III MM-020 RCT. This was a large international trial (1,600 patients) and was judged to be of good methodological quality, although it was open-label. The data from this trial can be considered mature as the final planned analyses of PFS and OS have been conducted. Continuous lenalidomide was statistically significantly superior to MPT on PFS, OS, tumour response, time to treatment failure, and time to progression. Expert clinical advice to the ERG considers that these improvements are clinically meaningful, particularly the increase in PFS (around four months) which is regarded to be important in the first line treatment of multiple myeloma. The PFS period is clinically considered to be associated with good HRQoL and better overall health and the aim is to prolong it as long as possible before initiation of subsequent line treatments.

There were statistically significant improvements in HRQoL in the trial for both Rd and MPT, with Rd overall having a slightly greater (but not statistically significant) improvement in EQ-5D during the 18 month assessment period. The CS suggests these are clinically significant based on published minimal important difference values. Expert clinical advice given to the ERG is that a meaningful improvement in HRQoL with lenalidomide would be expected given that thalidomide is regarded to have a poor toxicity profile. Rd showed statistical superiority to MPT in terms of the impact of side effects on HRQoL as measured by the EORTC QLQ-MY20 instrument at all time points except month 18. Overall, the ERG advises caution in the interpretation of HRQoL data as it is not clear how missing data were handled in the ITT analysis.

The proportion of patients with specific grade 3 or 4 adverse events (e.g. infections, metabolism and nutrition disorders) was higher for Rd than the Rd18 and MPT groups. Other events (e.g. blood and lymphatic system disorders, nervous system disorders), were experienced by a greater proportion of patients in the MPT group. Treatment emergent serious adverse events

were higher for Rd patients compared to Rd18 and MPT patients, which the CS suggests is due to the longer drug-exposure time in this arm.

Rd was superior to VMP in terms of PFS and OS as estimated indirectly from a NMA. The NMA itself was conducted according to methodological guidelines, though is limited by a sparse network of only four trials. The proportional hazards assumption does not appear to hold for PFS in the MM-020 trial. After 92 weeks the log cumulative hazard curves for Rd and MPT diverge. For OS the curves appear more parallel. The NMA was conducted using two different statistical approaches: one that assumed proportional hazards, and one based on fractional polynomials that produced time-varying hazard ratios. The company chose the proportional hazards NMA to inform their base case cost-effectiveness analysis. The ERG considers that the time varying hazard ratio NMA produces estimates with great uncertainty in some of the fractional polynomial models, including the one chosen by the company as best fitting. The ERG notes that OS, but not PFS, was one of the key drivers of cost-effectiveness. Furthermore, the ICERs for Rd versus VMP based on the fractional polynomials NMA were lower (i.e. less conservative). Taking all these factors into consideration the proportional hazards NMA therefore appears to be a more appropriate approach in this instance.

A comparison of Rd and VMP across other outcomes including tumour response, HRQoL and adverse events was not made, therefore it is not possible to estimate the similarities or differences between these two treatments on the broader range of clinically relevant outcomes.

7.2 Summary of cost effectiveness issues

The model structure for the economic evaluation is appropriate and consistent with the clinical disease pathway. The model contains health states of progression-free, progressed disease and death. A hybrid model is used with partitioned survival analysis for weeks <92 and a Markov model thereafter with transition probabilities between health states. The clinical evidence consists of the MM-020 trial for Rd and MPT. VMP is modelled by using the HR for PFS and OS compared to MPT from the company's NMA. The approach provided a good fit against the observed trial data from MM-020.

The company's base case results include a PAS for lenalidomide whereby lenalidomide is given free of charge after [redacted] cycles. The CS models produce an ICER of £[redacted] per QALY for Rd compared to MPT and £[redacted] per QALY for Rd compared to VMP. The company acknowledge

that Rd is not cost-effective against MPT and request that the comparison against VMP is most pertinent to this technology appraisal. The company's probabilistic sensitivity analyses showed there is a probability of [redacted] and [redacted] that Rd is cost-effective compared to VMP at willingness to pay thresholds of £20,000 and £30,000 per QALY respectively.

The ERG conducted two versions of the base case analyses. Version 1 includes changes to the time on treatment failure, HRQoL estimation and costs of administration of VMP. Version 2 is considered exploratory and includes all the changes in version 1 along with a change in subsequent treatments given after initial disease progression. Specifically, this version explores the impact on the cost effectiveness results when patients do not receive thalidomide as a subsequent treatment, and those receiving Rd initially would not receive Rd as a subsequent treatment. The ERG base case ICER for Rd compared to VMP in version 1 is £[redacted] per QALY gained (an increase of £[redacted] from the company's base case ICER). For the ERG base case version 2, the ICER is £[redacted] per QALY (a decrease of £[redacted] from the company's base case ICER). In summary, the ERG's preferred base case analysis increases the ICER from the company's base case analysis, but it remains within the willingness-to-pay threshold of £30,000 per QALY.

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9 APPENDICES

Appendix 1 - Company and ERG assessment of the NMA trials using the Cochrane Risk of Bias Assessment[38]

Judgements	Treatment	MM-020 (FIRST)[22 23 30 62 31 32] Rd, Rd18 & MPT	IFM 01/01 (Hulin 2009)[18] MP & MPT	IFM-99/06 (Facon 2007)[17] MP & MPT	VISTA[19-21] MP & VMP
Selection bias (Random sequence generation)	CS	Low risk	Unclear risk	Unclear risk	Unclear risk
	ERG	Low risk	Unclear risk	Unclear risk	Unclear risk
Comment: No details reported for IFM 01/01; IFM 99/06 and VISTA trials.					
Selection bias (Allocation concealment)	CS	Low risk	Low risk	Unclear risk	Unclear risk
	ERG	Low risk	Low risk	Unclear risk	Unclear risk
Comment: No details reported for IFM 01/01; IFM 99/06 and VISTA trials.					
Performance bias	CS	High risk	Unclear risk	Unclear risk	High risk
	ERG	High risk	Low risk	Unclear risk	High risk
Comment: The CS states that there is an unclear risk in performance bias in the IFM 01/01 and IFM 99/06 trial. As the IFM01/01 trial is placebo-controlled, the ERG considers that the risks for performance bias to be low risk.					
Detection Bias	CS	Low risk	Low risk	Low risk	Low risk
	ERG	High risk	Unclear risk (placebo controlled)	Unclear risk	High risk
Comment: The ERG consider risks of detection bias to be high for the MM-020 and VISTA trials due to the open-label nature of the studies.					
Attrition Bias	CS	Low risk	Low risk	Low risk	Low risk
	ERG	Low risk	Unclear risk	Unclear risk	Unclear risk
Comment: In IFM 01/01, a higher withdrawal rate from the thalidomide group due to toxicity compared to the placebo (n=48 vs 15) was recorded and it was not stated whether this was adjusted for. The ERG consider the risk for both IFM 01/01 and IFM 99/06 to be unclear as even though it was stated the ITT analysis was performed it was not adequately defined or stated whether missing data had to be accounted for and if so, how this was done. Within the VISTA trial, it was stated that discontinuations due to AEs were 37 in the					

bortezomib group and 35 in the control group. However, the ERG note that 19 additional discontinuations were recorded in the bortezomib group which would have resulted in an imbalance between trial arms. It unclear how this would have affected final analysis.					
Reporting bias	CS	Low risk	Unclear risk	Unclear risk	Unclear risk
	ERG	Low risk	Low risk	Low risk	Low risk
Comment: None					
Other bias	CS	Low risk	Low risk	High risk	Low risk
	ERG	Low risk	Low risk	Unclear risk	Low risk
Comment: The IFM-99/06 trial included patients aged between 65 and 75 years, but patients younger than 65 years were included if they were ineligible for high-dose treatment. It is unclear if this may have had an impact on the results, as baseline characteristics were only reported for the age ≥70 years. It is therefore unclear if trial arm were balanced with regards to age.					

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Lenalidomide for previously untreated multiple myeloma [ID474]

You are asked to check the ERG report from Southampton Health Technology Assessment Centre to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by the end of 15 January using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Systematic literature reviews

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 73 – "Of these, 644 studies were excluded, mainly as the studies were in a patient population not relevant to the decision problem."	Modification of statement to "Of these, 644 studies were excluded (51 of which were identified and excluded in the original search), mainly as the studies were in a patient population not relevant to the decision problem"	Statement could be misleading as 51 of the 644 studies that were excluded were duplicates generated by the overlapping dates used for the original and updated search.	Amendment made
Page 84 – "In a second stage of the review, the company excluded studies that were not relevant to the decision problem."	Removal of statement	This step was only conducted for the review of clinical studies hence the statement is incorrect (see Appendix H.1.1 of the CS).	Amendment made
Pages 44 & 127 – "the ERG considered that due to the open-label nature of the studies, the risk for detection bias was high for the MM-020 and VISTA trials"	Ensure statement is consistent with corresponding cell for VISTA in Appendix 1 which currently states "low risk" of detection bias, or vice versa.	Assessment of detection bias for VISTA on pages 44 & 127 and corresponding cell in Appendix 1 are inconsistent.	Amendment made

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 127 Appendix 1 – ERGs assessment of selection bias (Allocation concealment) for IFM 01/01 (Hulin 2009) is stated as "unclear risk"	Modification of ERGs assessment of selection bias (Allocation concealment) for IFM 01/01 (Hulin 2009) to "low risk"	The ERGs assessment of selection bias (Allocation concealment) for IFM 01/01 (Hulin 2009) does not reflect the Cochrane Handbook for Systematic Reviews of Interventions[1] which states that a publication stating "central randomization" was performed is considered to have a low risk of bias for the allocation concealment domain. As per Appendix D, Table 67 of the CS, the primary publication for this trial states, "This multicenter, placebo-controlled, phase III trial randomly assigned patients centrally in a 1:1 ratio."	Amendment made

Issue 2 Network meta-analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16 – "Of the two statistical methods used to conduct the NMA (constant hazards and fractional polynomials), the results of the fractional polynomial model varied according to which 'order' of model was chosen."	Modification of statement to "Of the two statistical methods used to conduct the NMA (constant hazard ratios and fractional polynomials), the results of the fractional polynomial model varied according to which 'order' of model was chosen."	This statement could be misleading because the method used does not explicitly assume constant hazards. This analysis is referred to as "constant hazard ratios NMA" elsewhere in the ERG report; the company proposes using this description throughout.	Amendment made

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16 – “The constant hazards statistical NMA appears to be the most appropriate model to inform the assessment as the results are associated with less uncertainty and the assumption of proportional hazards has been statistically confirmed”	Modification of statement to “The constant hazard ratios NMA appears to be the most appropriate model to inform the assessment as the results are associated with less uncertainty and the assumption of proportional hazards has been statistically confirmed”	This statement could be misleading because the method used does not explicitly assume constant hazards. This analysis is referred to as “constant hazard ratios NMA” elsewhere in the ERG report; the company proposes using this description throughout.	Amendment made
Page 44 – “The Bayesian constant hazards NMA was performed using a fixed effect regression model as described in the NICE Decision Support Unit technical support document number 2.”	Modification of statement to “The Bayesian constant hazard ratios NMA was performed using a fixed effect regression model as described in the NICE Decision Support Unit technical support document number 2.”	This statement could be misleading because the method used does not explicitly assume constant hazards. This analysis is referred to as “constant hazard ratios NMA” elsewhere in the ERG report; the company proposes using this description throughout.	Amendment made
Page 46 – “The ERG notes that HRs for OS and PFS generated by this model appear similar to those obtained from the constant hazards NMA”	Modification of statement to “The ERG notes that HRs for OS and PFS generated by this model appear similar to those obtained from the constant hazard ratios NMA”	This statement could be misleading because the method used does not explicitly assume constant hazards. This analysis is referred to as “constant hazard ratios NMA” elsewhere in the ERG report; the company proposes using this description throughout.	Amendment made

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 46 – "3.1.7.6 Choice between a constant hazards NMA and a time-varying fractional polynomials NMA"	Modification of statement to "3.1.7.6 Choice between a constant hazard ratios NMA and a time-varying fractional polynomials NMA"	This statement could be misleading because the method used does not explicitly assume constant hazards. This analysis is referred to as "constant hazard ratios NMA" elsewhere in the ERG report; the company proposes using this description throughout.	Amendment made
Page 48 – "The results of the time-varying fractional polynomial NMA, in terms of the basic parameter estimates from the second order FP model, are therefore used to justify the company's decision to use the constant hazards NMA"	Modification of statement to "The results of the time-varying fractional polynomial NMA, in terms of the basic parameter estimates from the second order FP model, are therefore used to justify the company's decision to use the constant hazard ratio NMA"	This statement could be misleading because the method used does not explicitly assume constant hazards. This analysis is referred to as "constant hazard ratios NMA" elsewhere in the ERG report; the company proposes using this description throughout.	Amendment made
Page 48 – "Taking all the above issues into consideration, the ERG believes that use of the constant hazards NMA as the primary analysis is appropriate in this instance."	Modification of statement to "Taking all the above issues into consideration, the ERG believes that use of the constant hazard ratios NMA as the primary analysis is appropriate in this instance."	This statement could be misleading because the method used does not explicitly assume constant hazards. This analysis is referred to as "constant hazard ratios NMA" elsewhere in the ERG report; the company proposes using this description throughout.	Amendment made

Issue 3 Description of sensitivity analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 103 – "the company performed a scenario analysis relating to OS where equal efficacy was assumed for VMP and MPT (including in subsequent therapy lines) which resulted in Rd dominating VMP"	Modification of statement to "the company performed a scenario analysis relating to OS where equal efficacy and subsequent therapy use was assumed for VMP and MPT which resulted in Rd dominating VMP"	This statement does not accurately reflect the scenario	Amendment made
Page 103 – "the company removed the treatment effect of Rd by assuming equal PPS for Rd and MPT."	Modification of statement to "the company removed the treatment effect of Rd in post-progression by assuming equal PPS for Rd and MPT"	The statement could be misleading as it does not specify that the treatment effect being equalised relates to PPS.	Amendment made
Page 105 Table 37 – ERG scenario 4ii has not been included in this table	Include associated description of "exclusion of lenalidomide from subsequent costs for Rd" in table	Table 37 does not provide an accurate description of ERG scenario 4	Amendment made
Page 110 – "ii. Exclusion of thalidomide from subsequent costs for Rd and VMP patients"	Modification of statement to "ii. Exclusion of thalidomide from subsequent costs for Rd and VMP patients, and exclusion of lenalidomide from subsequent costs for Rd""	This heading does not accurately reflect the scenario	Amendment made

Issue 4 ERG scenario 3i

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
VMP utility changes appear to have been applied inconsistently.	The VMP utility change applied in model cycle 7 (Utilities!S44 of the Excel model adapted by the ERG) should be 0.0287 (Utilities!Q50) rather than 0.0716 (Utilities!Q51).	The company's interpretation of the ERGs method for assigning utility changes is that VMP cycles (Utilities!P38:P45) were mapped to model cycles (Utilities!P47:P55), which were then rounded to the nearest whole model cycle. Based on this interpretation, the VMP utility change in model cycle 7 should be 0.0287 (model cycle 6, Utilities!P50) rather than 0.0716 (model cycle 8 [rounded to nearest whole cycle], Utilities!P51)	The ERG agrees with the amendment. We have updated the ERG report with the corrected utility value for VMP in cycle 7. This change in utility has a minimal impact on the ERG base case ICERs for Rd vs VMP (differences in previous ERG ICERs and the corrected ERG ICERs are less than £100).
Age-adjustment of the VMP utilities appears to have been applied incorrectly	In the Excel model adapted by the ERG, the VLOOKUP in Utilities!K39:539 should use the same age lookup value as for the pre-progression utility for Rd and MPT (i.e. column E rather than column F)	Based on the company's interpretation of the ERGs method, the age disutility for VMP should be applied as per Rd and MPT.	Not a factual error. The ERG adjusted the age look up values for VMP arm based on the VMP treatment cycle. Further, changing the lookup value (from column E to column F) has no impact on the utility values in column K as the age for Rd and MPT (in Column E) and that of VMP arm (in column F) takes the same age adjusted utilities in *'util.age.adjust.'*.

Issue 5 Typographical issues and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10 – "Patient cross-over between trial arms was not permitted during the trial, however, upon disease progression patients in both arms received subsequent lines of treatment with either the same or an alternative anti-myeloma treatment."	Modification of statement to "Page 10 – "Patient cross-over between trial arms was not permitted during the trial, however, upon disease progression patients in all arms received subsequent lines of treatment with either the same or an alternative anti-myeloma treatment.""	This statement may be misleading as the MM-020 trial is a three-arm study.	Amendment made
Page 10 – "At the 21st Jan 2016 data cut-off, Rd demonstrated a significant improvement of 10 months for median OS compared with MPT (HR 0.78; 95% CI 0.62–0.90; p=0.002)."	Modification of statement to "At the 21st Jan 2016 data cut-off, Rd demonstrated a significant improvement of 10 months for median OS compared with MPT (HR 0.78; 95% CI 0.67-0.92; p=0.002)"	Confidence intervals have been reported incorrectly (see page 53 and Figure 7 of the CS)	Amendment made
Page 15 – "[redacted] probability of cost-effectiveness at £30,000"	Modification of statement to "[redacted] probability of cost-effectiveness at £30,000"	Probability has been reported incorrectly (see page 142 of the CS)	Amendment made
Page 18 Table 3 – "ICER = £[redacted]"	Modification of ICER to "£[redacted]"	The company believes this is incorrect as it does not align with the incremental costs and QALYs in Table 3 or the ICER reported elsewhere in the ERG report	Amendment made

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21 – "It is unclear whether this dosage was the maximum dosage recommended for this indication."	Removal of statement	The SmPC states the starting dose for this indication is 25mg. This is highlighted in Table 2 and Appendix C of the CS	Amendment made
Page 39 – "No further detail appears to be given on the results of this exploratory analysis in the CS"	Removal of statement	Results of these analyses are provided in Appendix E Figures 33 and 34 of the CS	Amendment made
Page 51 – "30% reduction in the risk of disease progression or death for Rd (HR 0.70; 95% CI 0.60-0.81; p=0.00001)"	Modification of statement to "30% reduction in the risk of disease progression or death for Rd (HR 0.70; 95% CI 0.60-0.82; p=0.00001)"	Upper confidence interval reported incorrectly (see page 48 of the CS)	Amendment made
Page 58 – "TTF with Rd treatment was 2.8 months (median) longer compared with MPT treatment (16.9 months Rd; 14.1 months MPT; HR 0.75; no CI reported, p=0.00002)"	Modification of statement to "TTF with Rd treatment was 2.8 months (median) longer compared with MPT treatment (16.9 months Rd; 14.1 months MPT; HR 0.76; 95% CI 0.67–0.86, p=0.00002)"	The confidence intervals are reported in Section B.2.6.9 of the CS	Amendment made
Page 60 – "Fewer patients treated with Rd received second-line therapy compared with patients in the MPT group (55.9% Rd; 69.6% MPT)"	Modification of statement to ""Fewer patients treated with Rd received second-line therapy compared with patients in the MPT group (55.9% Rd; 69.7% MPT)"	Proportion of MPT patients receiving second-line therapy is incorrect (see Table 16 of the CS)	Amendment made
Page 63 – "…, clinically meaningful improvements at six and nine months for Rd compared to MPT were observed"	Modification of statement to "…, clinically meaningful improvements at six and twelve months for Rd compared to MPT were observed"	Second time-point is incorrect (see page 58 of the CS)	Amendment made

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 64 – "The Rd group showed statistically significant improvement in fatigue at months 3, 6 and 12 but not at month 18"	Removal of statement	Fatigue is not a domain of the EORTC QLQ-MY20. The company believes this statement was intended for Section 3.3.6.2.	Amendment made Text moved to Section 3.3.6.2
Page 72 – "…, which was around 8 weeks longer compared to the Rd18 group and around 13 weeks longer that the MPT group"	Modification of statement to "…, which was around 8 weeks longer compared to the Rd18 group and around 13 weeks longer that the MPT group, based on medians"	Statement could be misleading as it does not specify that differences in drug exposure times are based on medians for each treatment group	Amendment made
Page 77 – "The CS stated that owing to the inherent structural link between mortality and earlier progression events, it was inappropriate to model PFS and OS independently using a partitioned survival analysis"	Modification of statement to "The CS stated that owing to the inherent structural link between mortality and earlier progression events, it was more appropriate to model PFS and OS using a state transition approach"	This statement is misleading. The CS states that the structural link between health states was considered when selecting the modelling approach, and that the link between mortality and earlier progression events is not captured in partitioned survival models, however does not state that this renders a partitioned survival model inappropriate.	Amendment made
Page 83 – "The ERG therefore suggests that Rd and MPT should both use the same distribution for TTP…"	Modification of statement to "The ERG therefore suggests that Rd and MPT should both use the same distribution for TTF…"	This statement refers to time to treatment failure (TTF) rather than time to progression (TTP)	Amendment made
Page 97 Table 32 – "Total QALYs for Rd = [redacted]"	Modification of total QALYs for Rd to "[redacted]"	QALYs have been reported incorrectly (see Table 50 of the CS)	Amendment made

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 112 – "which is an increase of £[redacted] from the company's base case ICER"	Modification of statement to "which is an increase of £[redacted] from the company's base case ICER"	The increase in the ICER has been reported incorrectly	Amendment made

Issue 6 Referencing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 26 – "records at each stage of the SLR screening processes (CS Appendix D, Fig 25)"	Modification of statement to "records at each stage of the SLR screening processes (CS Appendix D, Fig 27)"	The cross-reference is incorrect	Amendment made
Page 26, Section 3.1.3, first paragraph – references for VISTA do not include San Miguel 2013[2] which reports the final data cut for OS which was used in the NMA.	Include the following reference; San Miguel JF, Schlag R, Khuageva NK et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. J Clin Oncol 2013;31:448–55.	The company suggests including this reference for clarity given San Miguel 2013 was used in the NMA of OS (see Appendix D.1.1.4 Table 62 of the CS)	Reference added
Page 29, Table 7 footer – "Table based on CS Table 12 in CS section B.2.13.2"	Modification of statement to "Table based on CS Table 12 in CS section B.2.3.7"	The cross-reference is incorrect	Amendment made

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 43, Section 3.1.7.1, first paragraph – list of references for studies included in the evidence network does not include San Miguel 2013[2] which reports the final data cut for OS used in the NMA	Include the following reference; San Miguel JF, Schlag R, Khuageva NK et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. J Clin Oncol 2013;31:448–55.	The company suggests including this reference for clarity given San Miguel 2013 was used in the NMA of OS (see Appendix D.1.1.4 Table 62 of the CS)	Reference added
Pages 53-67 – page numbers read as "Page 130 of 130"	Correct page numbers	Ensure alignment with cross-referencing in proforma	This does not appear in the master version of the document.
Page 55, Table 12 footer – "Reproduction of CS B.2.8.2 Table 20"	Modification of statement to "Reproduction of CS B.2.9.2 Table 20"	The cross-reference is incorrect	Amendment made
Page 57, Table 13 footer – "Reproduction of CS B.2.8.2 Table 18"	Modification of statement to "Reproduction of CS B.2.9.2 Table 18"	The cross-reference is incorrect	Amendment made
Page 73 – "The inclusion and exclusion criteria for the systematic review are presented in Table 18 in CS Appendix G.1.1"	Modification of statement to "The inclusion and exclusion criteria for the systematic review are presented in Table 72 in CS Appendix G.1.1"	The cross-reference is incorrect	Amendment made

References

1) Version 5.0.1 of the Cochrane Handbook for Systematic Reviews of Interventions*, *Higgins JPT, Altman DG (editors). Chapter 8: Assessing risk of biasies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008

2) San Miguel JF, Schlag R, Khuageva NK et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. J Clin Oncol 2013;31:448–55.

The steps to replace the lenalidomide complex patient access scheme (PAS) with a simple discount

Introduction

Celgene are replacing the existing complex PAS for lenalidomide (cycle cap scheme under which the drug cost for people who remain on treatment for more than 26 cycles is met by the company) with a confidential simple discount. Because a simple discount applies to all current and future indications, the discount level must ensure lenalidomide is cost-effective in the least cost-effective indication among those with positive National Institute for Health and Care Excellence (NICE) Guidance and those currently undergoing appraisals.

There are currently two suspended Final Appraisal Determinations (FADs) for ongoing appraisals of lenalidomide which were reviewed with the inclusion of the complex PAS with the cycle cap reduced to [redacted] cycles;

- ID667: Lenalidomide for treating multiple myeloma after 1 prior treatment with bortezomib (part rev TA171)[1]
- ID474: Lenalidomide in combination with dexamethasone for previously untreated multiple myeloma[2]

To ensure that lenalidomide remains cost-effective in these appraisals based on the simple discount, [redacted]. This was possible for ID474, but not for ID667 as it is not clear what the committee's decision making ICER or incremental NMB was (see Appendix 1, section 2.1 below). Therefore, the level of discount in ID667 was calculated [redacted].

The discount levels for these indications have been calculated using the models submitted in the respective NICE appraisals. The only changes made to the models (except for correcting a minor costing error identified in the model for ID474 where the administration cost of the cycle cap was applied irrespective of the number of patients on treatment) have been to remove the cycle cap and apply the simple discount to the list price of lenalidomide in its place. The updated models have been provided and the steps for removing the cycle cap and applying the simple discount for lenalidomide are presented in Appendix 1.

NICE has published positive guidance for lenalidomide in the following indications based on the currently operational 26 cycle cap:

- Multiple myeloma in people who have received two or more prior therapies (TA171)[3]
- Myelodysplastic syndromes (MDS) associated with an isolated deletion 5q cytogenetic abnormality (TA322)[4]

The discount required for lenalidomide to be cost-effective in these indications was calculated as the equivalent discount provided by the 26 cycle cap, based on the associated guidance and supporting documentation published on the NICE website.

Calculation of discount level for 'Multiple myeloma (newly diagnosed) – lenalidomide [ID474]'

In contrast to the Celgene base case, the Evidence Review Group (ERG) preferred[5, 6]:

- to assume time on treatment for bortezomib (VMP) is equal to thalidomide (MPT) and assume the same parametric distribution for MPT/VMP as the intervention (Weibull);
- lower administration costs for the comparator; and
- minor changes to the comparator utility

The level of discount required [redacted] is not affected by these changes, as they do not affect lenalidomide acquisition costs (Table 1). The discount level ([redacted]) is therefore reflective of the discount that was provided by the proposed [redacted] cycle cap.

Table 1: Newly diagnosed multiple myeloma (ID474) discount levels

Scenario	Incremental NMB (Rd vs. VMP) ([redacted], £)	ICER (Rd vs. VMP) (£ per QALY)	Discount required [redacted]
Celgene base case	[redacted]	[redacted]	[redacted]
Celgene base case [with correction]*	[redacted]	[redacted]	[redacted]
ERG base case (scenario 1, 3 & 5)	[redacted]	[redacted]	[redacted]
ERG base case (scenario 1, 3 & 5) [with correction]*	[redacted]	[redacted]	[redacted]

Key: ERG, evidence review group; NMB, net monetary benefit; Rd, lenalidomide plus dexamethasone; VMP, bortezomib plus melphalan plus prednisolone; [redacted]

Notes: *See Appendix 1, section 1.1 for further detail on the correction made

Calculation of discount level for 'Multiple myeloma – lenalidomide (post-bortezomib) (part review TA171) [ID667]'

As described in Appendix 1, section 2.1, an approach was taken in this appraisal which incorporated savings for patients in third line multiple myeloma (TA171) generated by reducing the cycle cap from 26 cycles to [redacted] cycles into the ICER calculation. The method for incorporating these savings when switching to the simple discount is also described in Appendix 1, section 2.2.

Since it is not clear what the decision-making incremental NMB was, the discount level required has been calculated [redacted] The associated discount level is [redacted] (Table 2).

Table 2: Multiple myeloma in people who have received one prior therapy (ID667) discount level

Incremental NMB ([redacted], £)	ICER (Rd vs. MP) (£ per QALY)	Discount required [redacted]
[redacted]	[redacted]	[redacted]
Key: MP, melphalan plus prednisolone; NMB, net monetary benefit; Rd, lenalidomide plus dexamethasone; [redacted]		

Indications where lenalidomide has positive NICE Guidance

MDS associated with an isolated deletion 5q cytogenetic abnormality (TA322)

[redacted]

[redacted]

Multiple myeloma in people who have received two or more prior therapies (TA171)

[redacted]

Summary

If a simple discount were to be applied across all indications, the discount level that would result in lenalidomide being cost-effective [redacted]

For the suspended appraisals (ID474 and ID667), this discount level is sufficient to replace the proposed [redacted] cycle cap upon which the committee had based their decisions and produced FADs (see Table 3 below). The ICERs generated by the simple discount level of [redacted] are as follows;

- ID474 Celgene base case: £11,886 per QALY
- ID474 ERG preferred base case: £19,654 per QALY
- ID667 base case: [redacted] per QALY

The simple discount level of [redacted] would come into effect at the point of release of the suspended FADs.

Table 3: Simple discount compared to equivalent discounts offered by the complex PAS (capping scheme)

TA (or ID) number	Indication	Discount offered by the complex PAS in cost-effectiveness modelling	New simple discount offered
TA171	Multiple myeloma in people who have received two or more prior therapies	[redacted]	[redacted]
TA322	Transfusion-dependent anaemia caused by low or intermediate-1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate	[redacted]	[redacted]
ID667***	Patients with multiple myeloma who are ineligible for transplant, unsuitable for thalidomide and have received bortezomib at 1st line	[redacted]	[redacted]
ID474***	Transplant-ineligible newly diagnosed multiple myeloma for patients who are unable to tolerate or have contraindications to thalidomide	[redacted]	[redacted]
Key: TA, Technology Appraisal; * with End of Life criteria met at an ICER of £43,800 per QALY ** [redacted], not matching incremental NMB or discount provided by cycle cap *** cap proposed at [redacted] cycles not at 26 cycles			

Appendix 1 - Methods

[redacted]

[redacted]

[redacted]

[redacted]

References

1. National Institute for Health and Care Excellence. Multiple myeloma - lenalidomide (post bortezomib) (part rev TA171) [ID667]. 2018. (Updated: 22 March 2018) Available at: https://www.nice.org.uk/guidance/indevelopment/gid-tag452. Accessed: 15 November 2018.
2. National Institute for Health and Care Excellence. Multiple myeloma (newly diagnosed) - lenalidomide [ID474]. 2018. (Updated: 22 March 2018) Available at: https://www.nice.org.uk/guidance/indevelopment/gid-tag429. Accessed: 15 November 2018.
3. National Institute for Health and Care Excellence. Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. 2009. (Updated: 01 April 2014) Available at: https://www.nice.org.uk/guidance/ta171. Accessed: 15 November 2018.
4. National Institute for Health and Care Excellence. Final appraisal determination: Lenalidomide for treating myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality. 2014. (Updated: 24 September 2014) Available at: https://www.nice.org.uk/guidance/ta322/documents/myelodysplastic-syndrome-deletion-5q-lenalidomide-id480-final-appraisal-determination-document2. Accessed: 15 November 2018.
5. Southampton Health Technology Assessments Centre (SHTAC). Evidence Review Group Report: Lenalidomide in combination with dexamethasone for previously untreated multiple myeloma. 22 December 2017 2017. Data on File.
6. National Institute for Health and Care Excellence. Multiple myeloma (newly diagnosed) – lenalidomide [ID474]: Pre-meeting briefing. 31 January 2018 2018. Data on File.
7. Kleijnen Systematic Reviews Ltd in collaboration with Erasmus University Rotterdam and Maastricht University. Lenalidomide for the treatment of myelodysplastic syndromes associated with deletion 5q cytogenetic abnormality: Addendum to Evidence Review Group's Report following Celgene's new evidence submission with approved patient access scheme of 8th November 2013. 2013. Available at: https://www.nice.org.uk/guidance/ta322/documents/myelodysplastic-syndrome-deletion-5q-lenalidomide-evaluation-report2. Accessed: 15 November 2018.
8. National Institute for Health and Care Excellence. Final appraisal determination: Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. 2009. Available at: https://www.nice.org.uk/guidance/ta171/documents/multiple-myeloma-lenalidomide-final-appraisal-determination3. Accessed: 15 November 2018.
9. Peninsula Technology Assessment Group (PenTAG). The clinical- and cost-effectiveness of lenalidomide for multiple myeloma in people who have received at least one prior therapy: An evidence review of the submission from Celgene (Addendum to the report submitted on 1st September 2008). 2008. Available at: https://www.nice.org.uk/guidance/ta171/documents/addendum-to-the-erg-report2. Accessed: 15 November 2018.
10. National Institute for Health and Care Excellence. Final appraisal determination: Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy. 2016. Available at: https://www.nice.org.uk/guidance/ta428/documents/final-appraisal-determination-document. Accessed: 15 November 2018.

CONFIDENTIAL

Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Lenalidomide in combination with dexamethasone for previously untreated multiple myeloma

ERG response to Celgene's new patient access scheme (PAS)

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Date completed **25th March 2019**

Celgene have agreed to replace the existing complex Patient Access Scheme (PAS) for lenalidomide (whereby the company proposes to pay the cost of lenalidomide for any treatment beyond 26 cycles) with a confidential simple discount of [redacted].

The company have made changes to the economic model to incorporate the simple discount. The simple discount was applied to the intervention arm for first-line and subsequent lines of lenalidomide but not applied to the use of lenalidomide in subsequent lines of the comparator arm. The company stated that this reflects current practice where the 26 cycle cap is applied. NICE confirmed that this approach was correct. In addition, the company corrected an error in the model relating to the cost of applying the cycle cap. The cost of applying the cycle cap should have applied when patients were receiving lenalidomide beyond the cycle cap, proportional to the number of patients on treatment.

The ERG checked and verified the company's results with the new simple PAS and found that it had been correctly implemented. We present a comparison of the company's and the ERG's original base case (based on the proposed PAS cap at [redacted] cycles) and the revised base case results (based on a simple PAS discount) in Table 1 and Table 2.

Table 1 Comparison of the cost-effectiveness results for company's base case

Company's original base case with proposed PAS cap at [redacted] cycles			
Treatments	**Total costs**	**Total QALYs**	**ICER (per QALY)**
VMP	[redacted]	[redacted]	
Rd	[redacted]	[redacted]	[redacted]
Company's original base case with proposed PAS cap at [redacted] cycles (corrected)*			
Treatments	**Total costs**	**Total QALYs**	**ICER (per QALY)**
VMP	[redacted]	[redacted]	
Rd	[redacted]	[redacted]	[redacted]
Company's revised base case (corrected) with simple PAS			
Treatments	**Total costs**	**Total QALYs**	**ICER (per QALY)**
VMP	[redacted]	[redacted]	
Rd	[redacted]	[redacted]	£11,886

VMP = bortezomib, melphalan and prednisone; Rd = lenalidomide and dexamethasone

*Correcting the estimation whereby the cost of applying cycle cap was applied appropriately

Table 2 Comparison of the cost-effectiveness results for ERG base case

ERG's original base case with proposed PAS cap at [redacted] cycles			
Treatments	**Total costs (£)**	**Total QALYs**	**ICER (per QALY)**
VMP	[redacted]	[redacted]	
Rd	[redacted]	[redacted]	[redacted]
ERG's original base case with proposed PAS cap at [redacted] cycles (corrected)*			
Treatments	**Total costs (£)**	**Total QALYs**	**ICER (per QALY)**
VMP	[redacted]	[redacted]	
Rd	[redacted]	[redacted]	[redacted]
ERG's revised base case (corrected) with simple PAS			
Treatments	**Total costs (£)**	**Total QALYs**	**ICER (per QALY)**
VMP	[redacted]	[redacted]	
Rd	[redacted]	[redacted]	£19,654

VMP = bortezomib, melphalan and prednisone; Rd = lenalidomide and dexamethasone

*Correcting the estimation whereby the cost of applying cycle cap was applied appropriately

The ERG includes a scenario analysis where the simple PAS discount is applied for the use of lenalidomide in both the intervention and comparator arms. This is implemented in the model by adjusting the post-progression treatment cost for lenalidomide (Excel cell Drug Costs! L106) by the PAS discount. The results are shown in Table 3 below for the ERG base case, and produce an ICER of £26,713 per QALY. The company's base case results with the simple PAS discount give an ICER of £18,986 per QALY (Table 4).

Table 3 ERG scenario analysis: Simple PAS applied to intervention and comparator arms for all lines of lenalidomide for the ERG base case

Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER incremental (£/QALY)**
VMP	[redacted]	[redacted]			
Rd	[redacted]	[redacted]	[redacted]	[redacted]	£ 26,713

VMP = bortezomib, melphalan and prednisone; Rd = lenalidomide and dexamethasone

Table 4 ERG scenario analysis: Simple PAS applied to intervention and comparator arms for all lines of lenalidomide for the company's base case

Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER incremental (£/QALY)**
VMP	[redacted]	[redacted]			
Rd	[redacted]	[redacted]	[redacted]	[redacted]	£ 18,986

VMP = bortezomib, melphalan and prednisone; Rd = lenalidomide and dexamethasone