NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [ID1477]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [ID1477]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** **and** **final stakeholder list** are available on the NICE website.

1. **Company submission** from **Sanofi**

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Myeloma UK
   b. UK Myeloma Forum (UKMF)
   c. NHS England

4. **Expert personal perspectives** from:
   a. Mr Alan Chant – patient expert nominated by Myeloma UK
   b. Ms Shelagh McKinlay – patient expert nominated by Myeloma UK
      Ms McKinlay indicated that she supported the UK Myeloma Forum statement
   c. Professor Gordon Cook – clinical expert nominated by the UK Myeloma Forum
      Professor Cook indicated that he supported the UK Myeloma Forum statement
   d. Dr Neil Rabin – clinical expert nominated by Sanofi – summary of discussions with the NICE technical team

5. **Evidence Review Group report** prepared by **the School of Health and Related Research, University of Sheffield (ScHARR)**
   the Evidence Review Group report was updated after the factual accuracy check

6. **Evidence Review Group – factual accuracy check**

7. **Technical Report**

8. **Technical engagement response** from **Sanofi**
   a. Response form
   b. Appendices

9. **Technical engagement responses from experts:**

a. Dr Neil Rabin – clinical expert, nominated by Sanofi

10. Technical engagement response from consultees and commentators:

a. Myeloma UK
b. Janssen

11. Evidence Review Group critique of company response to technical engagement prepared by **the School of Health and Related Research, University of Sheffield (ScHARR)**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma

[ID1477]

Document B

Company evidence submission

March 2020

File name	Version	Contains confidential information	Date
ID1477_Isatuximab_Document B_02032020_FINAL_REDACTED	FINAL	Yes	2nd March 2020

Contents

Abbreviations

ADA	Anti-drug antibody	**MAb**	Monoclonal antibody
ADCC	Antibody-dependent cellular cytotoxicity	**MAIC**	Matching adjusted indirect comparisons
AE	Adverse event	**MCM**	Markov cohort model
AESI	Adverse event of special interest	**MDRD**	Modification of Diet in Renal Disease
AFT	Accelerated failure time	**MDS**	Myelodysplastic syndrome
AL	Amyloid-light	**MDT**	Maximum tolerated dose
ALT	Alanine aminotransferase	**MedDRA**	Medical Dictionary for Regulatory Activities
ANC	Absolute neutrophils count	**MM**	Multiple myeloma
ASCT	Autologous stem cell transplant	**MR**	Minimal response
AST	Aspartate aminotransferase	**MRD**	Minimum residual disease
AUC	Area under the curve	**MRenal**	Minor renal response
AWMSG	All Wales Medicines Strategy Group	**MRU**	Medical resource utilisation
AWTTC	All Wales Therapeutics & Toxicology Centre	**NA**	Not applicable
BCC	Basal cell carcinoma	**NC**	Not calculable
BIC	Bayesian Information Criterion	**NCI-CTCAE**	National Cancer Institute - Common Terminology Criteria for Adverse Events
BM	Bone marrow	**NHS**	National Health Service
BOR	Best overall response	**NICE**	National Institute for Health and Care Excellence
BSC	Best supportive care	**NMA**	Network meta-analysis
CA	Chromosomal abnormalities	**NR**	Not reported
CADTH	Canadian Agency for Drugs and Technologies in Health	**PanVd**	Panobinostat, bortezomib, dexamethasone
CBR	Clinical benefit rate	**PCSA**	Potentially clinically significant abnormalities
CD38	Cluster of differentiation 38	**PD**	Progressive disease
CDC	Complement-dependent cytotoxicity	**Pd**	Pomalidomide, low-dose dexamethasone
CDF	Cancer drugs fund	**PH**	Proportional hazard
CEA	Cost-effectiveness analysis	**PFS**	Progression free survival
CEAC	Cost-effectiveness acceptability curve	**PI**	Proteasome inhibitor
CFB	Change from baseline	**PIM**	Promising Innovative Medicine
CHMP	Committee for Medicinal Products for Human Use	**PK**	Pharmacokinetic
CI	Confidence interval	**PO**	Per Os (Oral administration)
CR	Complete response	**Pom**	Pomalidomide
CrCl	Creatinine clearance	**PPS**	Post-progression survival
CRenal	Complete renal response	**PR**	Partial response
CTD	Cyclophosphamide, thalidomide, dexamethasone	**PS**	Performance status
CUA	Cost-utility analysis	**PSA**	Probabilistic sensitivity analysis

Dara	Daratumumab	**PSM**	Partitioned survival model
DARA	Daratumumab monotherapy	**PT**	Preferred term
DaraVd	Daratumumab, bortezomib, low dose dexamethasone	**QALY**	Quality-adjusted life year
DOR	Duration of response	**QoL**	Quality of life
DRMM	Double relapsed and/or refractory multiple myeloma	**QW**	Weekly
DSA	Deterministic sensitivity analysis	**Q2W**	Every two weeks
DSU	Decision Support Unit	**R**	Restricted
DTL	Dose-limiting toxicity	**RBC(s)**	Red blood cell(s)
ECG	Electrocardiogram	**RCS**	Restricted cubic spline
ECOG	Eastern Cooperative Oncology Group	**RCT**	Randomised controlled trial
eCRF	Electronic case report form	**RD/d**	Lenalidomide, /low dose dexamethasone
EOL	End of life	**RDI**	Relative dose intensity
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire with 30 items	**R-ISS**	Revised International Staging System
EORTC-QLQ-MY20	European Organisation for Research and Treatment of Cancer Quality of Life Multiple Myeloma Specific Module with 20 items	**RMST**	Restricted mean survival time
EOT	End of treatment	**RRMM**	Relapsed and/or refractory multiple myeloma
EQ-5D-5L	Euro QoL Group self-report questionnaire with 5 dimensions and 5 levels per dimension	**SA**	Sensitivity analysis
EMA	European Medicines Agency	**SAE**	Serious adverse event
EPd	Elotuzumab, pomalidomide, low dose dexamethasone	**SCC**	Squamous cell carcinoma
ERG	Evidence review group	**sCR**	Stringent complete response
ESS	Effective sample size	**SCT**	Stem cell transplant
FCE(s)	Finished consultant episode(s)	**SMC**	Scottish Medicines Consortium
FDA	US Food & Drug Administration	**SmPC**	Summary of product characteristics
FISH	Fluorescence in situ hybridisation	**SOC**	System Organ Class
FLC	Free light chain	**SPE**	Serum protein electrophoresis
FU	Follow-up	**SPMs**	Second primary malignancies
G-CSF	Granulocyte-colony stimulating factor	**STC**	Simulated treatment comparison
GEE	Generalised estimating equation	**TEAEs**	Treatment-emergent adverse events
GHS	Global health status	**TLS**	Tumour lysis syndrome
GvHD	Graft vs host disease	**TNT**	Time to next treatment
HIV	Human immunodeficiency virus	**TSD**	Technical Support Document
HLGT	High level group term	**TTBR**	Time to best response
HRQoL	Health-related quality of life	**TTD**	Time to discontinuation

HSCT	Haematopoietic stem cell transplants	**TTDTD**	Time to definitive treatment discontinuation
HR	Hazard ratio	**TTO**	Time-trade-off
IAT	Indirect anti-globulin test	**TTP**	Time to progression
ICER	Incremental cost-effectiveness ratio	**Tx**	Treatment
IFE	Immunofixation	**ULN**	Upper limit of normal
IMiDs	Immunomodulatory drugs	**V**	Bortezomib
IMWG	International Myeloma Working Group	**VCD**	Bortezomib, cyclophosphamide, dexamethasone
IPCW	Inverse probability of censoring weighting	**Vd**	Bortezomib, low dose dexamethasone
IPD	Individual patient data	**VGPR**	Very good partial response
IRs	Infusion reactions	**VMP**	Bortezomib, melphalan, prednisone
IRC	Independent Response Committee	**VTD**	Bortezomib, thalidomide, dexamethasone
IRT	Interactive response technology	**WOCBP**	Woman of childbearing potential
IsaP(om)d	Isatuximab, pomalidomide, low-dose dexamethasone	**WTP**	Willingness-to-pay
ISS	International Staging System	Lines of therapy	
ITC	Indirect treatment comparison	**3L**	3rd Line (Patients who have received two prior lines of treatment)
ITT	Intention-to-treat	**4L**	4th Line (Patients who have received three prior lines of treatment)
IV	Intravenous	**4L+**	4th Line (Patients who have received three or more prior lines of treatment)
IxaRd	Ixazomib, lenalidomide, low dose dexamethasone		
kd	Carfilzomib, low dose dexamethasone		
KM	Kaplan-Meier		
LDH	Lactate dehydrogenase		
Len	Lenalidomide		
LLN	Lower limit of normal		
LY	Life year		

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

B.1.1 *Decision problem*

The objective of this technology appraisal is to evaluate the clinical and cost-effectiveness of isatuximab, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed / refractory multiple myeloma who have received at least 2 lines of prior therapies including lenalidomide and proteasome inhibitor.

The submission covers the technology's full marketing authorisation for this indication but focuses on the intended patient group expected to be treated with isatuximab in UK clinical practice. The decision problem addressed in this submission is largely in line with the scope issued by NICE and is summarised 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	Adult patients with RRMM who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor, and whose disease progressed on the last therapy	Adult patients with RRMM who have received three prior therapies, including lenalidomide and a proteasome inhibitor, and whose disease progressed on the last therapy (corresponds to 4L treatment of MM in the UK).	The population of interest reflects the anticipated place of isatuximab in UK clinical practice and area of high unmet need.
Intervention	Isatuximab in combination with pomalidomide and low-dose dexamethasone	As per scope	—
Comparator(s)	For people who have had ≥3 prior lines of therapy (in accordance with NICE recommendations): • Pomalidomide in combination with dexamethasone	For people who have had 3 prior lines of therapy (base case) (4L): • Pomalidomide in combination with dexamethasone For people who have had ≥3 prior lines of therapy (supplementary analysis) (4L plus): • Pomalidomide in combination with dexamethasone	This comparison reflects the most appropriate comparator based on the anticipated place in therapy for isatuximab. • Supplementary analysis is provided to meet requirement of the NICE scope only.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	For people who have had two previous lines of therapy (in accordance with NICE recommendations): • Panobinostat in combination with bortezomib and dexamethasone For people who have had ≥3 prior lines of therapy (in accordance with NICE recommendations): • Panobinostat in combination with bortezomib and dexamethasone	PanVd is not considered a relevant comparator to IsaPd as defined in the NICE scope. However, in order to meet the requirements of the scope we have conducted an economic analysis of IsaPd vs. PanVd. This is based on a matched adjusted indirect comparison (MAIC) in the absence of a connected network to PanVd. This presented as an exploratory analysis in Appendix K.4 to meet requirements of the NICE scope.	Feedback from clinical experts during a Sanofi Advisory Board (1) have indicated that this combination appears to be reserved for later line (i.e. ≥5th line) mainly due to its associated toxicities. This view is supported by market share data acquired by Sanofi (2). Similar views have been documented in previous NICE submissions (TA427, TA510) (3, 4).
Outcomes	• Progression-free survival • Overall survival • Response rates • Duration of response • Time to progression • Time to next treatment • Adverse effects of treatment • Health-related quality of life	In addition to the outcomes in the NICE scope, we also present evidence on time-to-discontinuation (TTD)	TTD is used to estimate treatment duration (and therefore treatment costs of IsaPd and the comparators Pd and PanVd) in the economic analysis

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
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 will be considered	The economic base case is based on the NICE reference case. However, this submission also presents a cost per life-year gained (LYG) analysis	In patients with end stage disease there is evidence that extension to life dominates quality of life. Therefore, we present cost/LYG analysis
Subgroups to be considered	—	The clinical section of the submission presents evidence from all pre-specified subgroups, in accordance with the proposed license	—

Abbreviations: CDF, Cancer Drugs Fund; CUA, cost-utility analysis; DSU, Decision Support Unit; IsaPd, isatuximab, pomalidomide, low dose dexamethasone; LYG, life-year gained; MAIC, matching-adjusted indirect comparison; MM, multiple myeloma; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PanVd, panobinostat, bortezomib, dexamethasone; Pd, pomalidomide, low dose dexamethasone; PFS, progression-free survival; RRMM, relapsed or refractory multiple myeloma; TTD, time-to-discontinuation.

B.1.2 *Description of the technology being appraised*

Table 2: Technology being appraised

UK approved name and brand name	UK approved name: Isatuximab Brand name: Sarclisa®
Mechanism of action	Isatuximab is a humanised monoclonal antibody which binds to cell surface glycoprotein CD38. This may trigger antitumor ADCC, CDC, inhibition of enzymatic activity, and apoptosis, eventually leading to cell lysis in CD38-expressing tumour cells
Marketing authorisation/CE mark status	Regulatory submission to EMA: The application was submitted on 30th April 2019. CHMP positive opinion expected in Q1 2020 Marketing authorisation: regulatory approval expected in Q2 2020
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Expected indication: Isatuximab is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and proteasome inhibitor and have demonstrated disease progression on the last therapy. Isatuximab is contraindicated in patients with hypersensitivity to the active substance or to any of its excipients (sucrose, histidine hydrochloride monohydrate, histidine, Polysorbate 80, water for injection)
Method of administration and dosage	**Isatuximab** Method of administration/dosage: 10 mg/kg IV infusion, weekly for four weeks (days 1, 8, 15 and 22), then every two weeks. The use of isatuximab is recommended in combination with pomalidomide and dexamethasone (methods of administration/dosage described below) **Pomalidomide** Method of administration/dosage: 4 mg PO, on Days 1 to 21 of each 28-day cycle **Dexamethasone** Method of administration/dosage: 40 mg (or 20 mg if the patient ≥75 years old) PO or IV, on Days 1, 8, 15 and 22 of each 28-day cycle. Dexamethasone should be used prior to isatuximab IV infusion to reduce the risk and severity of infusion reactions (IRs)
Additional tests or investigations	• Isatuximab binds to CD38 on RBCs and may result in a false positive IAT. Thus, to avoid potential problems with RBCs transfusion, patients receiving isatuximab treatment should have blood type and screen tests performed prior to the first isatuximab infusion; phenotyping may be considered prior to starting isatuximab treatment as per local practice • Isatuximab may be incidentally detected by SPE and IFE assays used for the clinical monitoring of M-protein. Thus, serum samples from patients treated with isatuximab may be tested by mass spectrometry (MS) to separate isatuximab's signal from the myeloma M-protein signal *NOTE: These tests are typical for anti-CD38 drugs and unlikely to incur additional costs to the NHS.*

<table>
<tr><td>List price and average cost of a course of treatment</td><td>Isatuximab list price: [redacted] (100 mg vial); [redacted] (500 mg vial)
The average total cost of IsaPd based on list prices are shown below. The drug costs are calculated for a 73 kg adult; costs are based on time-to-discontinuation ([redacted] months) and the relative dose intensity (from ICARIA-MM):<table><tr><th>Drug</th><th>List price (based on a 73 kg adult, [redacted] months TTD, RDI from ICARIA-MM)</th></tr><tr><td>Isatuximab</td><td>[redacted]</td></tr><tr><td>Pomalidomide</td><td>£102,299</td></tr><tr><td>Dexamethasone</td><td>£921</td></tr><tr><td>Total cost of combination</td><td>[redacted]</td></tr></table></td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>A PAS has been agreed for isatuximab with the Department of Health and Social Care. The scheme is a simple discount of [redacted] of the list price for isatuximab

Isatuximab PAS price: [redacted] (100 mg vial); [redacted] (500 mg vial)

Drug costs for a 73 kg adult treated with IsaPd (based on average time-to-discontinuation [[redacted] months], RDI from ICARIA-MM and assumed [redacted] PAS on pomalidomide):<table><tr><th>Drug</th><th>PAS price (based on a 73 kg adult, [redacted] months TTD, RDI from ICARIA-MM)</th></tr><tr><td>Isatuximab</td><td>[redacted]</td></tr><tr><td>Pomalidomide</td><td>[redacted]</td></tr><tr><td>Dexamethasone</td><td>£921</td></tr><tr><td>Total cost of combination</td><td>[redacted]</td></tr></table></td></tr>
</table>

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; CD 38, cluster of differentiation 38; CDC, complement-dependent cytotoxicity; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; IAT, indirect antiglobulin test; IFE, immunofixation electrophoresis; IV, intravenous; MM, multiple myeloma; PAS, patient access scheme; PO, oral; MS, mass spectrometry; RBCs, red blood cells; RDI, relative dose intensity; SPE, serum protein electrophoresis; TTD, time-to-discontinuation.

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

- Multiple myeloma (MM) is a malignant, progressive and incurable haematopoietic tumour of plasma cells, characterised by the neoplastic proliferation of clonal plasma cells that produce monoclonal immunoglobulins (5)
- MM is an orphan disease with an incidence of approximately 9.3/100,000 population in England (6) and although 80% of patients are aged 60 years or greater, the majority are under 75 years old (6)
- Patients with MM report a high symptom burden and there is a drastic impact on patients' quality of life (QoL), as well as that of families or carers (7-11)
- MM is characterised by cycles of remission and relapse, with decreasing treatment response after each relapse (12-15), In general, patients diagnosed with MM will receive an average of 4 to 8 different regimens during their remaining lifespan. However, once a patient becomes refractory to those agents, survival is limited, and newer treatment options are needed
- Life expectancy (median overall survival [OS]) of patients with RRMM (i.e. the patient group which is the subject of this submission) is 7.9 months to 15.2 months (16, 17)

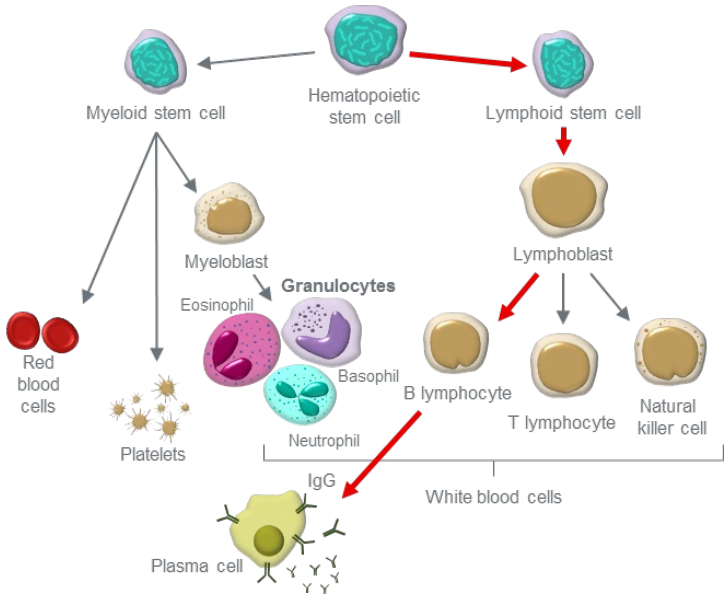
Isatuximab, in combination with pomalidomide and dexamethasone (IsPd), is proposed for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received 3 prior lines of treatment (including lenalidomide and a proteasome inhibitor [PI]) and have demonstrated disease progression on the last therapy. In UK clinical practice this would place IsaPd as treatment option at 4L alongside treatments such as pomalidomide and panobinostat. Clinical outcomes reported in Section B2 demonstrate that IsaPd leads to unprecedented increase progression-free survival time over current treatments

- In this population there is a particularly high unmet need since, despite available treatments, treatment outcomes remain poor, with median progression-free survival (PFS) and OS at 4L is less than 2 years

B.1.3.1 *Disease overview*

Multiple myeloma (MM) is a malignant, haematopoietic tumour of plasma cells (Figure 1), characterised by a clonal proliferation of bone marrow plasma cells (5). The term MM refers to the presence of more than one site of affected bone at the time of diagnosis. Myeloma cells produce large quantities of an abnormal immunoglobulin, known as M-protein or paraprotein (18). The abundantly produced paraprotein causes organ and tissue impairment (19), manifesting as anaemia, bone pain, renal impairment and hypercalcaemia, as well as lowering immunity, leading to recurrent infections (5, 19).

Figure 1: Origin of plasma cells



Adapted from National Cancer Institute (20)

This submission focuses on those patients with relapsed and refractory MM (RRMM). RRMM is defined as disease that becomes non-responsive while on therapy, or which progresses within 60 days of last therapy in patients who have achieved minimal response or better at some point before progressing in their disease course (21). Within RRMM, we highlight evidence (where available) for patients who have had 3 prior lines of anti-myeloma treatments, including lenalidomide, (4L), as this is the anticipated place in therapy for isatuximab in UK clinical practice.

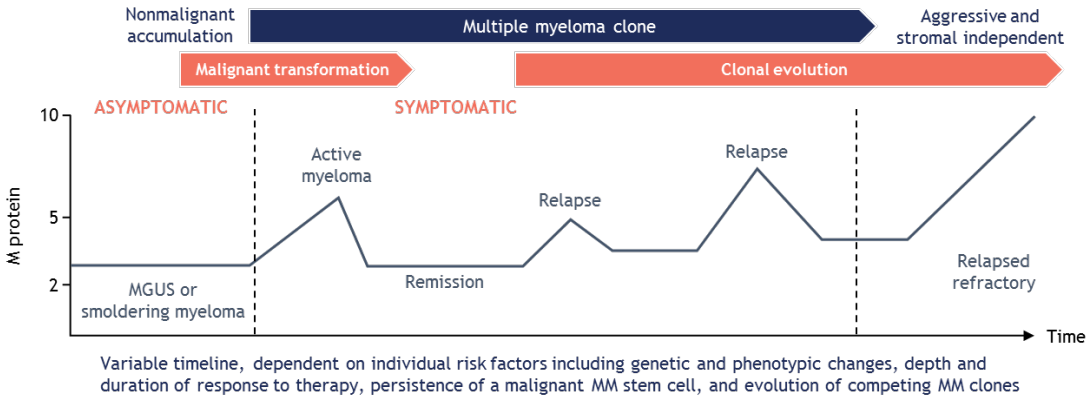
B.1.3.1.1 Epidemiology

Although MM is the second most common hematologic malignancy worldwide (22, 23), it is a rare disease: In 2015, the age-standardised incidence in England was 9.3/100,000 population (6). This is considerably higher than the reported global age-standardised incidence-rate of 2.1/100,000 population (24). MM was the 19th most common cancer in the UK in 2015 (6). The incidence of MM is highest in the elderly, peaking around the age of 85-89 years, with 45% of cases diagnosed in patients aged ≥75 years (6). More men than women are affected by MM (6) and is also more common in black than in white people (25). In line with expectations around population ageing (26), the incidence of MM has been steadily rising over the last two decades – the UK incidence in 1993 was around 7.2/100,000 population (6). Based on cross-sectional chart review data from seven EU countries, including the UK, 15% of patients are expected to reach 4L, equating to 602 adult patients per year (15), demonstrating the high rate of progression to later lines of treatment. Of these, approximately 70% patients are considered eligible for antibody treatment (see Company Budget Impact Analysis).

B.1.3.1.2 Clinical burden

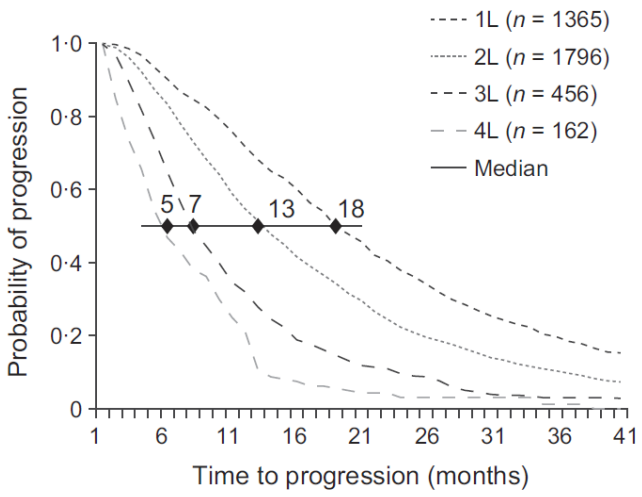
The disease course of MM is outlined in Figure 2. MM is often preceded by monoclonal gammopathy (in the asymptomatic stage) (27) and is characterised by cycles of remission and relapse, with decreasing treatment response after each relapse (12-15). Time to progression has been reported to decrease from 18 months, at 1st line treatment, to five months after 4L treatment by Yong et al, 2016 (15) (Figure 3), in line with progression-free survival being reported to decrease from 11 months, after 1st line treatment, to seven months at 4L treatment by Jagannath et al, 2016 (13). Overall survival decreases as patients progress to subsequent lines of therapy, and is poor in patients who have received two or more lines of therapy, with a median overall survival of 7.9 months to 15.2 months (Figure 9) (16, 17) (see Section B.1.3.2 for further details on overall survival). Refractory status has a considerable impact on overall survival, based on real-world data (17) (Figure 4).

Figure 2: MM disease course



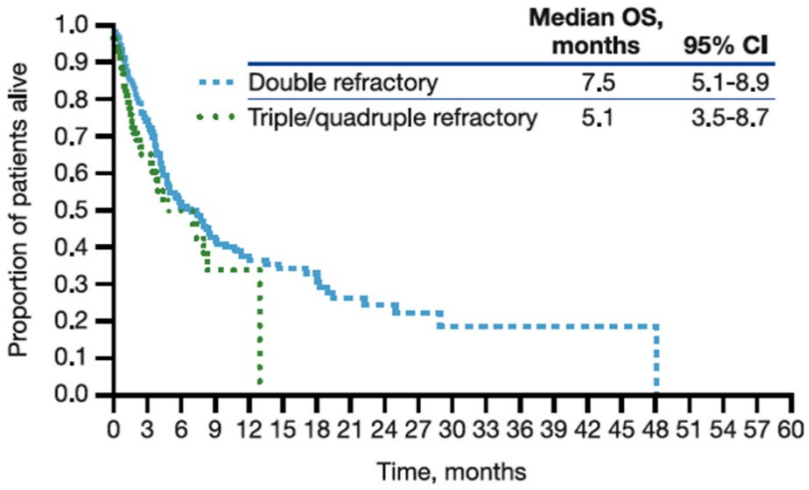
From Kurtin et al, 2013 (12)
Abbreviations: MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma.

Figure 3: Time to progression by line of treatment



From Yong et al, 2016 (15)

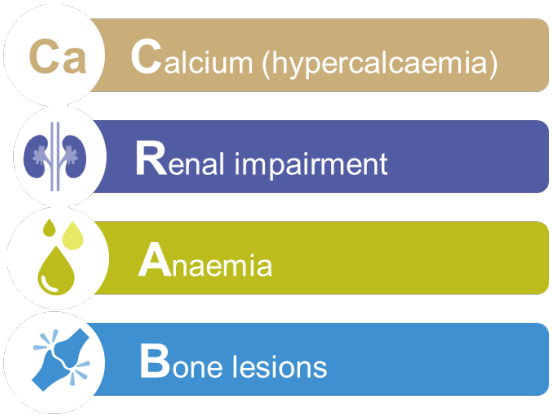
Figure 4: Median OS in patients with ≥3 lines of therapy, based on refractory status



From Usmani et al, 2016 (17)
Abbreviations: CI, confidence interval; OS, overall survival.

Multiple myeloma is progressive and remains incurable in the majority of cases (12, 28, 29). The characteristic features of MM are referred to as CRAB features (Figure 5) (27). If untreated, hypercalcaemia can lead to renal insufficiency (30). Patients with MM also experience recurrent infections, most likely due to impaired immune response resulting from neutropenia and/or insufficient levels of normal antibodies (30). Bone lesions manifest as lytic lesions, osteoporosis or fractures (30), and may affect as many as 90% of patients over the course of the disease (31).

Figure 5: CRAB features of MM

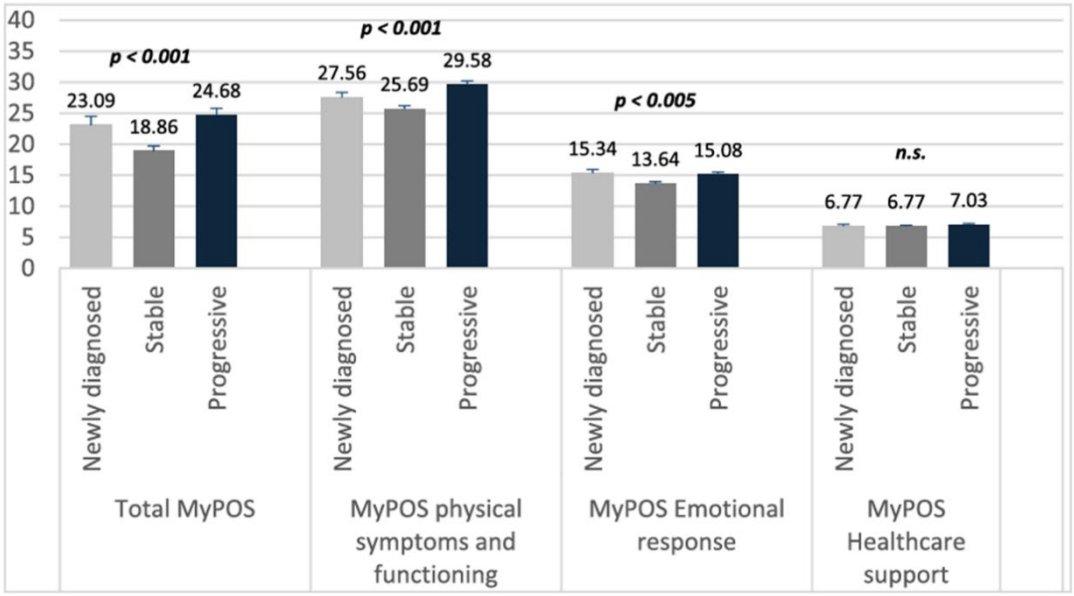


Based on Rajkumar et al, 2014 (27)
Abbreviation: MM, multiple myeloma

Approximately 10% of patients with MM are affected by primary systemic amyloidosis (30), where amyloid bodies are deposited in the heart, kidney, gastrointestinal tract, nerves, skin, joints, and blood vessels (32), which can result in organ failure (33). Typical symptoms of primary systemic amyloidosis include fatigue, purpura, enlarged tongue, diarrhoea, oedema, and lower-extremity paraesthesia (33).

The incidence of renal disease and cardiovascular disease increases as patients receive more lines of therapy, progressing to relapsed and/or refractory disease (34). Overall, patients with relapsed/progressive disease report a higher number of symptoms than newly-diagnosed patients or patients in a treatment-free interval, indicating a higher symptom burden (Figure 6) (11). Compared with newly diagnosed or treatment-free patients with MM, more patients with relapsed/progressed MM suffer from shortness of breath (p=0.002), constipation (p=0.018), mouth problems (p=0.007) and tingling of hand/feet (p<0.001) (11).

Figure 6: Differences in the total MyPOS and MyPOS subscales in three phases of myeloma disease



From Ramsenthaler et al, 2016 (11)
Abbreviation: MyPOS, Myeloma Patient Outcome Scale.
The MyPOS determines point prevalence of disease- and treatment-related symptoms and measures palliative care concerns, with higher score indicating higher needs.

B.1.3.1.3 Impact on quality of life

Multiple myeloma has a drastic impact on patients' quality of life, with each relapse causing a considerable burden on their emotional and physical well-being and social interactions, with an extended effect on their families or carers (7-11).

Patients face a wide range of MM-related symptoms, which has a negative impact on their quality of life (QoL) (7, 9, 11). Fatigue, bone pain and tiredness are the most commonly quoted symptoms, with patients reporting difficulty in taking long walks or carrying out strenuous activities even during low-severity phases of MM (7, 9, 11). Increased severity of symptoms is associated with substantial impaired HRQoL (9). In a European multicentre cohort study, in patients with MM or relapsed and/or refractory MM across four different severity level subgroups (i.e. asymptomatic, mildly symptomatic, moderately symptomatic, or severely symptomatic), each disease severity level was associated with a reduction of ≥6 points in the average score of the distribution of HRQoL (i.e., 'Global Health Status' domain within the EORTC instrument, 'QoL, 'Physical, Functioning', 'Social Functioning' and 'Future Perspective') from the previous

symptom level, indicating the negative impact of advancement of the disease on the QoL, physical, and social functioning of the patients (9).

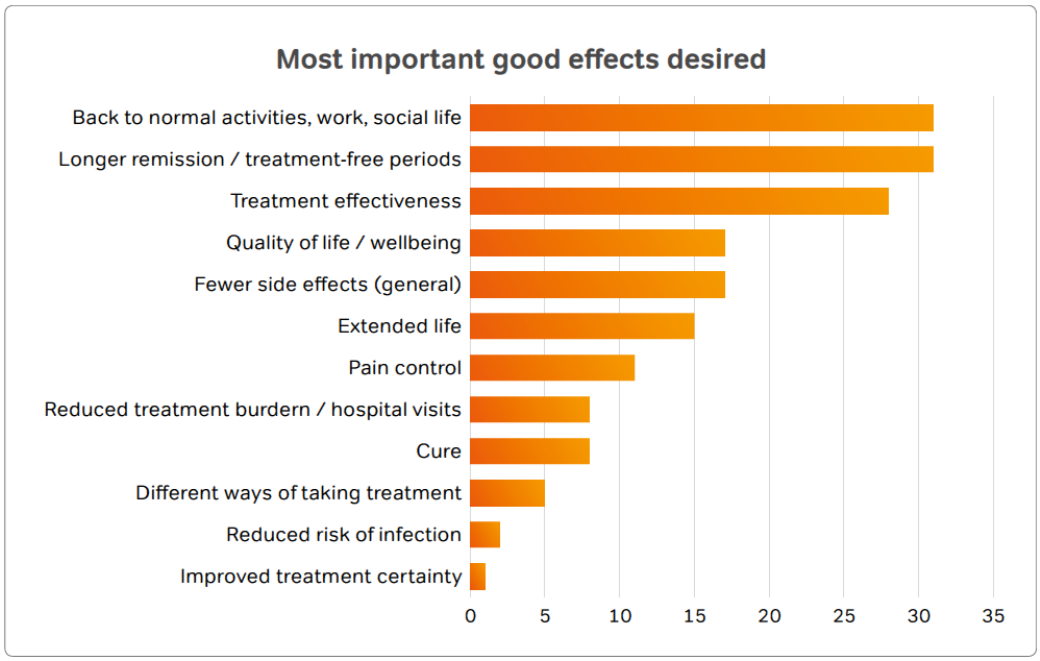
Treatment-related toxicity, accumulating over time, poses an additional burden on patients with relapsed and/or refractory MM (35). The use of multi-drug regimens for the treatment of relapsed MM and of maintenance therapy during the stable disease periods, contribute to a cumulative burden on patients (35). New therapies enable many patients to live for 5–10 years beyond diagnosis, but adverse events resulting from treatments can often affect their QoL (35). These treatment-related toxicities, when combined with MM symptoms/co-morbidities and ageing (MM is most prevalent in patients older than 70 years), may contribute to impairment of QoL through reduction of physical, psychological and social functioning (35).

The effect of coping with the symptoms of MM and the inevitable mortality in the absence of a cure result in poor functioning and mental health problems in many patients (10, 11). Results from a systematic review and meta-analysis, including thirty-six studies, showed that many patients with MM experience symptoms of depression, anxiety, and worries about dying/the future, with more than half of the patients reporting decreased emotional and social functioning (pooled prevalence of 57.7% [95% CI; 12.5, 92.9] and 58% [95% CI; 12.2, 93.2], respectively) (10).

Moreover, relapsed and/or refractory MM can negatively affect the social functioning of patients due to their inability to perform the same level of activities they used to perform (8). Patients' families also experience emotional and physical burden, having to emotionally deal with the relapsed disease, in addition to undertaking activities the patients cannot do themselves and accompanying them to the hospital/clinic visits (8).

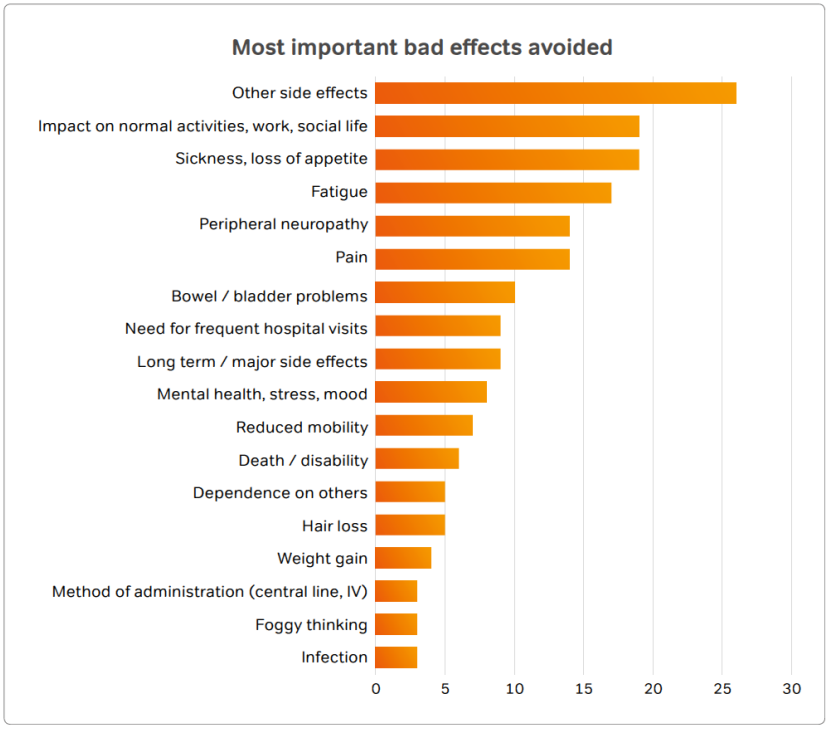
NICE performed a survey among patients with MM (97 respondents) to better understand the patient experience and preferences of patients with MM (36). The report found that patients valued their ability to perform normal activities and longer remission periods most, followed by treatment effectiveness and QoL (Figure 7). The most burdensome aspects of MM treatment were found to be other side effects, the impact on normal activities, sickness/loss of appetite and fatigue (Figure 8).

Figure 7: Treatment effects most desired by patients with MM who responded to the survey



From NICE, 2019 (36)

Figure 8: Treatment effects least desired by patients with MM who responded to the survey



From NICE, 2019 (36)

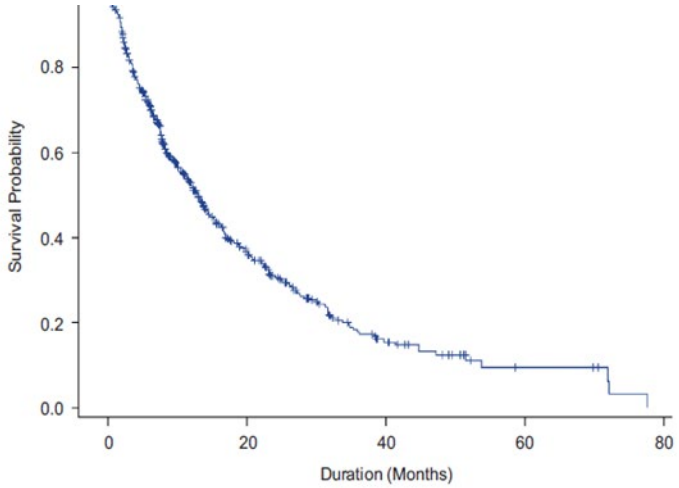
B.1.3.2 *Life expectancy*

Multiple myeloma is generally incurable and fatal (12, 28, 29). The 5- and 10-year survival rates of adults with MM in England and Wales are 47% and 33%, respectively (37); the median OS of patients with MM remains around five years (38).

As noted above, OS decreases(Figure 9) as patients progress to subsequent lines of therapy, (Figure 3 and Figure 4) (16, 17). Patients who are refractory to multiple lines of treatments have very poor survival outcomes. Double refractory (3L) patients have a median OS of 7.5 months (Figure 4); triple (4L) refractory or quadruple (4L+) refractory patients have median OS of 5.1 months (Figure 4). These data are in line with those of a retrospective audit performed by the Haematological Malignancy Research Network (HMRN) (39), which estimated the OS for patients receiving third-line therapy at 1.1 years (95% CI 0.8, 1.4). It is reasonable to deduce that the OS for patients receiving 4L treatment will be worse than for those at 3L, suggesting that median OS in 4L remains considerably less than 2 years. The short life expectancy at 4L has been accepted as part of the justification to apply the EoL multiplier for the purposes of decision making by NICE committees when appraising previous HTA submissions in RRMM (3, 4, 40, 41). This is discussed in Sections B.1.3.3 and B.1.3.7.

Isatuximab, in the indication under review and in its anticipated place in therapy, therefore meets the life-expectancy criterion set by NICE for end-of-life treatments (i.e. usually <24 months) (42).

Figure 9: Overall survival in patients with MM from diagnosis of refractory MM



Time zero (T0): time when patients (n=543) met criteria for refractoriness defined as no response or progress on therapy or within 60 days of stopping the drug-containing regimen.
Source: Kumar et al, 2017 (16)
Abbreviation: MM, multiple myeloma.

B.1.3.3 *Clinical pathway of care as per NICE guidance*

The treatment pathway for MM in the UK (Figure 10) is complex, with a large variety of combinations available to clinicians and patients depending on eligibility and response to treatment. This can result in patients receiving a varied treatment sequence and making them eligible for different treatment combinations with each relapse (relevant NICE

guidance and clinical guidelines for the management MM, are presented in Sections B.1.3.5. and B.1.3.6).

As there is currently no cure for MM, patients receiving available treatments eventually relapse. While treatment options have grown for first-line treatment and for those following a single relapse, for patients who have received three prior lines of treatments, including lenalidomide, there is a limited number of treatment options recommended by NICE (Figure 10):

- Panobinostat in combination with bortezomib and dexamethasone (PanVd) is recommended by NICE after two or three previous therapies (i.e. 3L and 4L) and via routine commissioning (39)
- Pomalidomide in combination with a low dose of dexamethasone (Pd is recommended by NICE in 4L and via routine commissioning (4)
- Daratumumab monotherapy (DARA) which is recommended by NICE for use in patients after three previous therapies and via the CDF (3)

Despite recent advances in treatment and improvements to the treatment pathway, there are limited treatment options for patients who are refractory to lenalidomide in the 3L and 4L setting. These heavily pre-treated patients have a poor prognosis and a short life expectancy (see Section B.1.3.2). The short life expectancy at 4L has been accepted by previous NICE committees when appraising the Pd and DARA submissions (3, 4). Treatment-related toxicities further contribute to the burden of RRMM (35). All these data highlight the need for additional treatment options.

B.1.3.4 *Isatuximab place in therapy*

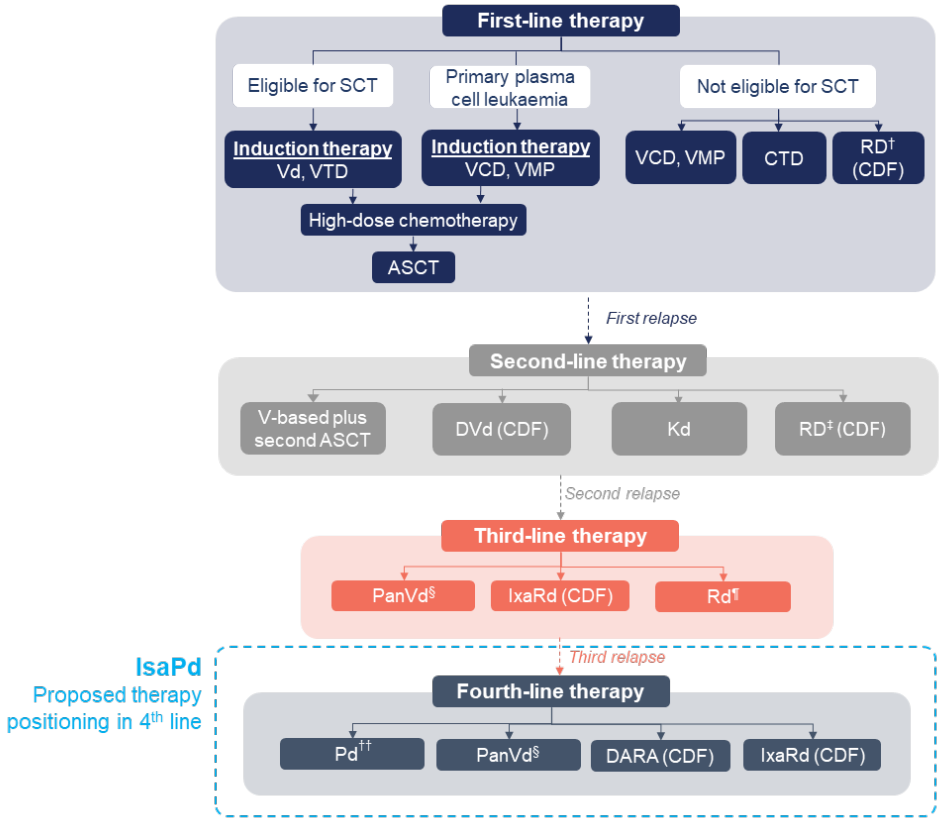
Isatuximab is a new an anti-CD38 monoclonal antibody (mAb) with a unique binding site and mechanism of action. Isatuximab targets a specific epitope of CD38, distinct from the binding sites of other anti-CD38 monoclonal antibodies (mAbs). The ongoing randomised Phase III trial (ICARIA-MM) has shown that isatuximab in combination with pomalidomide and a low dose of dexamethasone (IsaPd), significantly extends PFS, without significant additional AEs (43, 44),while preserving patients' QoL vs pomalidomide and a low dose of dexamethasone (Pd) (43).

In England and Wales, it is anticipated that IsaPd will be used in patients who have received three prior lines of treatment (i.e. 4L), including lenalidomide, for the following reasons:

- To be eligible for IsaPd treatment patients must have already received lenalidomide and a PI treatment. In England/Wales, lenalidomide (in combination with low dose dexamethasone) is recommended by NICE at 3L, and, according to market research, is generally used at 3L (45, 46)
- Pd (the comparator in ICARIA-MM) is recommended by NICE and used in patients who are at their third or subsequent relapse (4L+) and have received lenalidomide and bortezomib previously (4)

- Clinical expert opinion sought during Sanofi Advisory Board supports a 4L positioning based on unmet need (1)

Figure 10: Clinical pathway of management for MM with proposed positioning for IsaPd after failure with three prior lines of therapy, including lenalidomide and PI given alone or in combination



Source: adapted from NICE guideline on diagnosis and management of myeloma [NG35] (47)
Abbreviations: ASCT, autologous stem cell transplant; CDF, Cancer Drugs Fund; CTD, cyclophosphamide, thalidomide, dexamethasone; DARA, daratumumab monotherapy; DVd, daratumumab, bortezomib, low dose dexamethasone; IsaPd, isatuximab, pomalidomide, low dose dexamethasone; IxaRd, ixazomib, lenalidomide, low dose dexamethasone; kd, carfilzomib, low dose dexamethasone; PanVd, panobinostat, bortezomib, dexamethasone; PI, proteasome inhibitors; Pd, pomalidomide, low dose dexamethasone; Rd, lenalidomide, low-dose dexamethasone; RD, lenalidomide, dexamethasone; SCT, stem cell transplant; V, bortezomib; VCD, bortezomib, cyclophosphamide, dexamethasone; VD, bortezomib, low dose dexamethasone; VMP, bortezomib, melphalan, prednisone; VTD, bortezomib, thalidomide, dexamethasone; †If lenalidomide is contra-indicated to/not tolerated by the patient and if the manufacturer provides lenalidomide according to the commercial agreement. ‡If patients have received only one previous therapy, which included bortezomib, and if the manufacturer provides lenalidomide according to the commercial agreement. §Panobinostat provided by the manufacturer at the discount agreed in the patient access scheme. ¶Drug cost of lenalidomide for patients who remain on treatment for more than 26 cycles must be met by the manufacturer. ††Pomalidomide provided by the manufacturer at the discount agreed in the patient access scheme.

B.1.3.5 *Relevant NICE guidance, pathways or commissioning guides*

B.1.3.5.1 NICE guidance

For patients who experience relapsed or refractory disease with ≥2 prior lines of therapy:

- NICE guideline. Myeloma: diagnosis and management (NG35). February 2016. This guideline covers the diagnosing and managing of myeloma in people aged 16 and over (47)

- NICE technology appraisal in development. Elotuzumab for multiple myeloma (ID966). Expected date of issue to be confirmed.

B.1.3.6 *Clinical guidelines*

- NICE guideline. Myeloma: diagnosis and management (NG35). February 2016. This guideline covers the diagnosis and management of MM in people aged 16 and over (47)

- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016. This guideline covers integrated diagnostic reporting for diagnosing haematological cancer in adults, young people and children (48)

- British Society for Haematology (BSH) and UK myeloma Forum (UKMF). Guidelines for screening and management of late and long-term consequences of myeloma and its treatment. This guideline focuses on key the late effects in long-term patients with MM, providing recommendations on the use of screening protocols for early detection of late effects, and effective intervention strategies to improve the management of these patients (35)

- British Committee for Standards in Haematology (BCSH) and UK Myeloma Forum (UKMF). Guidelines for the diagnosis and management of Multiple Myeloma. 2014. These updated guidelines provide a national consensus of the haematological community in the UK, on the diagnosis and management of patients with MM (49)

- European Society for Medical Oncology (ESMO). Multiple Myeloma: ESMO clinical practice guidelines. These updated guidelines cover diagnosis, staging and risk assessment, treatment recommendations and response evaluation of MM (50)

- European Myeloma Network Guidelines. European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. This guidance provides recommendations for the front-line treatment of newly diagnosed patients with MM, based on the GRADE system for level of evidence (51)

B.1.3.7 *Issues relating to current clinical practice*

Although the treatment landscape for MM is continuously evolving there are still issues associated with current clinical practice.

- **In spite of existing treatment options at 4L, there is an unmet need for further efficacious treatments for patients who have received on lenalidomide**

Almost half of patients diagnosed with MM will receive three or more different regimens during their lifespan (52), utilising agents such as proteasome inhibitors (e.g., bortezomib, ixazomib and carfilzomib), immune modulatory agents (e.g. thalidomide, lenalidomide and pomalidomide), monoclonal antibodies (daratumumab and elotuzumab), histone deacetylase (HDAC) inhibitors (panobinostat) alone or in combination. The therapeutic goals for patients with RRMM, focusing on controlling the disease as effectively as possible, while prolonging survival and preserving functioning/QoL (53-55), are often not met, and further treatment options would improve the management of RRMM.

In Figure 10 it can be seen that there are options, albeit limited, for patients who have received 3 prior lines of treatment, but their efficacy is limited. Market research conducted by Sanofi with 50 UK haematologists who completed an online survey relating to treatment outcomes in clinical practice. According to survey results, patients treated at 4L typically have a PFS of 6–7months and an OS of 11 months (DARA: 7 months PFS and 10.6 months OS; Pd: 6.6 months PFS and 10 months OS). In comparison with existing options at 4L (pomalidomide and daratumumab), IsaPd offers substantially longer PFS and OS (56).

In the pivotal trial of DARA, median PFS and OS of 4 months and 20.1 months, respectively, are reported.

In the initial Phase III TOURMALINE-MM1 (TMM1) study, ixazomib in combination with lenalidomide and dexamethasone (IxaRd) had a reported median PFS of 20.6 months but, at a median follow-up of approximately 23 months, the median OS had not been reached in either treatment arms (57). However, in a regional follow-up study of TMM1, in China, the reported median PFS and OS were 6.7 months and 25.8 months, respectively (58).

Both DARA and IxaRd are only reimbursed via the CDF and as such are excluded as relevant comparators in this appraisal. IxaRd is also not a relevant comparator because, to be eligible for treatment with IsaPd, patients must have received lenalidomide. This is not the case for the IxaRd combination. Therefore, the patient population for IsaPd is different from that of IxaRd.

PanVd has a reported median PFS and OS of 12.5 months and 25.5 months (in patients who had received at least two previous prior regimens, including bortezomib and an immunomodulatory drug [IMiD]), respectively (59, 60). In the NICE scope, PanVd has been identified as a relevant comparator to IsaPd. However, clinical experts consulted during Sanofi Advisory Boards (1) have indicated limited use of this combination at 4L due to its associated toxicities. In clinical practice clinicians have told us that PanVd is reserved for later lines (e.g 5^{th} line) where patients are expected to have limited capacity to benefit to the extent suggested by PFS and OS data from PANORAMA-2. This view is supported by market share data acquired by Sanofi (46) and has been documented in previous NICE submissions (4, 61).

Pomalidomide in combination with a low dose of dexamethasone, has a reported median PFS of 4–4.4 months and a median OS of 12.7–16.8 months (Phase III–Phase II) (62-

64). Prior to daratumumab being made available through the CDF, nearly half of the patients received pomalidomide in combination with dexamethasone at 4L (46).

DARA, IxaRd and PanVd are not relevant comparators in this appraisal. Pomalidomide is the most relevant comparator to IsaPd as it the treatment most likely to be displaced in clinical practice. As such this submission presents the base case as the clinical and cost-effectiveness evidence comparing IsaPd to Pd. All clinical inputs for the economic model are derived directly from the ICARIA-MM trial for patients who received 3 prior lines of treatments, including lenalidomide.

A comparison with PanVd, based on a matching-adjusted indirect comparison (MAIC), is provided in order to meet the requirements of the NICE scope. However, PanVd is unlikely to be displaced by IsaPd, as it appears to be used in later lines (5th line) or to be limited by its toxicity.

- **Short life expectancy for RRMM, combined with treatment-related toxicities and co-morbidities**

Despite the substantial improvement in patient outcomes with newer therapies, once a patient becomes refractory to those agents, survival is limited; MM remains an incurable disease, with life expectancy for RRMM less than two years (17, 65). Relapse in MM is common; in a study by Yong et al, 2016 (15), in which nearly 5,000 patient records were reviewed across Europe, the median duration for 1st line treatment was 6 months, followed by a median treatment free interval of 10 months. Both treatment duration and treatment-free interval was found to reduce over time as patients progressed to further lines of therapy. An increase in toxicities and co-morbidities was also observed in later treatment lines, likely leading to treatment discontinuation (15).

B.1.3.8 *Conclusion*

MM is a malignant and incurable blood cancer affecting primarily the elderly. The disease inevitably progresses and is characterised by cycles of remission and relapse. With decreasing treatment response after each relapse (12-15), decreased OS with increasing treatment line (16, 17), and increasing burden associated with progression/relapse and being refractory to treatment (in RRMM) (11), the disease has a poor prognosis and a significant impact on patient's QoL. Life expectancy (median OS) of patients with RRMM (i.e. the patient group which is the subject of this submission) is less than two years (16, 17), thus meeting one of the criteria for NICE end-of-life (EOL) threshold. In spite of recent advances in management, clinical outcomes have largely remained the same, with median OS still below 2 years. For patients who are heavily pre-treated having received 3 prior lines including lenalidomide, treatment options are even more limited. Therefore, this is a need for new triplet treatments which can improve survival while maintaining QoL.

B.2. Clinical effectiveness

Isatuximab has been granted Orphan drug status by EMEA and awarded Promising Innovative Medicines status by the MHRA.

The results of study EFC14335 (ICARIA-MM trial) show that IsaPd treatment significantly improves PFS and ORR vs Pd in ITT population

This Phase III, prospective, open-label, multicentre, multinational, randomised, parallel group, double-arm study has shown that, at a median follow-up of 11.6 months:

- Treatment with IsaPd significantly prolonged PFS compared with Pd (median PFS: 11.53 months vs 6.47 months; HR of 0.596 [95% CI; 0.436, 0.814]; p=0.001). PFS benefit was consistent across all major subgroups
- A statistically significant improvement in ORR was shown in patients who received IsaPd compared with Pd (60.4% vs 35.3%; p<0.0001). A consistent improvement in ORR was observed across the pre-specified subgroups
- At the cut-off date, OS was immature (99 death events) but a trend to OS improvement in IsaPd (vs. Pd) was observed either in the overall ICARIA-MM population or in patients at 4L of treatment
- Quality-of-life as measured by EORTC-QLQ-C30 GHS score was sustained over time and similar in both treatment groups, either in the overall ICARIA-MM population, or in patients at 4L of treatment

Post hoc analyses of ICARIA-MM trial outcomes in patients with three prior lines of therapy, have found that IsaPd treatment (anticipated place in therapy at 4L) substantially improves clinical and quality of life outcomes

- In the 4L population (N=58 and N=52 in the Pd and IsaPd arms, respectively), median PFS was prolonged in the IsaPd arm (13.31 months [95% CI; 7.425, not calculable [NC]) in comparison with the Pd arm (7.82 months [95% CI; 4.468, 11.072]) (Figure 3). The stratified hazard ratio was 0.598 (95% CI; 0.348, 1.030) representing a 40.2% risk reduction of disease progression or death in favour of IsaPd vs Pd
- At the cut-off date, a total of 34 deaths were reported among patients at 4L of treatment (11 in IsaPd arm and 23 in Pd arm). Although OS was considered immature at this stage, a trend towards longer OS in IsaPd (vs Pd) was observed (HR of 0.494; [95% CI; 0.240, 1.015]), with a median OS of 14.36 months in the Pd arm while in the IsaPd it had not been reached
- ORR for patients in 4L, was numerically better in the IsaPd arm than in the Pd arm (53.8% vs 46.6%; p=0.3991)
- Quality-of-life as measured by EORTC-QLQ-C30 GHS score was sustained over time and similar in both treatment groups, in patients at 4L of treatment

Despite high level of censored data, clinically relevant outcomes are reported in the ITT population and patient with three prior lines of treatment (anticipated treated population in practice).

B.2.1 *Identification and selection of relevant studies*

B.2.1.1 *Search strategy*

A systematic literature review (SLR) was conducted to identify clinical evidence regarding the efficacy and safety of isatuximab and other relevant comparators for the treatment of RRMM in adult patients who have received at least two lines of treatment.

The methodology used for the SLR including the search strategy, databases searched, and selection criteria is presented in Appendix D. A summary of the inclusion and exclusion criteria is shown in Table 3. As this SLR was designed to be broad enough to serve a global context, comparators were included that may not be considered relevant to NICE. In line with the final scope, the intervention and comparators considered as relevant for this submission include: isatuximab + pomalidomide + dexamethasone (Isa-Pd), panobinostat + bortezomib + dexamethasone (PanVd) and pomalidomide + dexamethasone (Pd).

Table 3: Summary of the eligibility criteria for the clinical SLR

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adults (over 18 years of age) diagnosed with RRMM (including Kahler disease, myelomatosis, plasma cell myeloma and medullary plasmacytoma) who have received at least two lines of treatment Data provided on any subgroups were collected. Studies of mixed populations (e.g. studies including patients with one or more lines of prior treatment) were eligible if outcomes were reported separately for the population of interest (i.e. patients with two or more lines of prior treatment) or if 80% or more of the population was eligible.	• Children (under 18 years of age) • Patients not described as having RRMM • Patients who have had less than two lines of treatment (e.g. newly diagnosed)
Intervention	Isatuximab in combination with pomalidomide and dexamethasone (Isa-Pd)	
Comparators	Studies that compared the following interventions (as single agents or in combination) against each other, best supportive care or placebo for the treatment of RRMM were eligible overall: • Bortezomib (Bort) • Carfilzomib (Car) • Daratumumab (Dara) • Dexamethasone (Dex (high dose)/dex (low dose)) • Elotuzumab (Elo) • Ixazomib (Ixa) • Lenalidomide (Len) • Melphalan • Panobinostat (Pan) • Pomalidomide (Pom) • Thalidomide (Thal) • Vorinostat (Vor)	

Clinical effectiveness	Inclusion criteria	Exclusion criteria
	• Bendamustine (Ben) For the purpose of this submission, only studies assessing the following interventions were eligible: • Isa-Pd • PanVd • Pd	
Outcomes	• Progression free survival (PFS) • Overall survival (OS): all-cause survival and disease-specific survival • Time to progression (TTP) • Response outcomes: overall response rate (ORR), complete response, very good partial response (VGPR) and partial response • Duration of response (DoR) • Time on treatment • Time to next treatment • Treatment free interval • Adverse effects (AEs): any grade 3 or higher AE, serious AEs (SAE), withdrawals due to AE • Discontinuations • Mortality • Health related quality of life (HRQoL) outcomes and patient reported outcome (PRO) measures: EORTC-QLQ-C30, MY20, EQ-5D-5L/EQ-5D-3L, measures of patient satisfaction	
Study design	Prospective phase II–IV randomised controlled trials (RCTs)	Phase I clinical trials, non-comparative, retrospective studies, observational studies and case reports
Limits	English language since 2000†	

† Bortezomib (Velcade) was approved in 2003 and therefore the 2000 date limit was selected to ensure that the pivotal trials of bortezomib were identified.
Abbreviations: Dara, daratumumab; DaraPd, daratumumab+pomalidomide+ dexamethasone; EPd, elotuzumab+ pomalidomide+ dexamethasone; IsaPd, isatuximab+ pomalidomide+ dexamethasone; PanVd, panobinostat+ bortezomib+ dexamethasone; Pd, pomalidomide+ dexamethasone; RRMM, relapsed and refractory multiple myeloma

B.2.1.2 *Study selection*

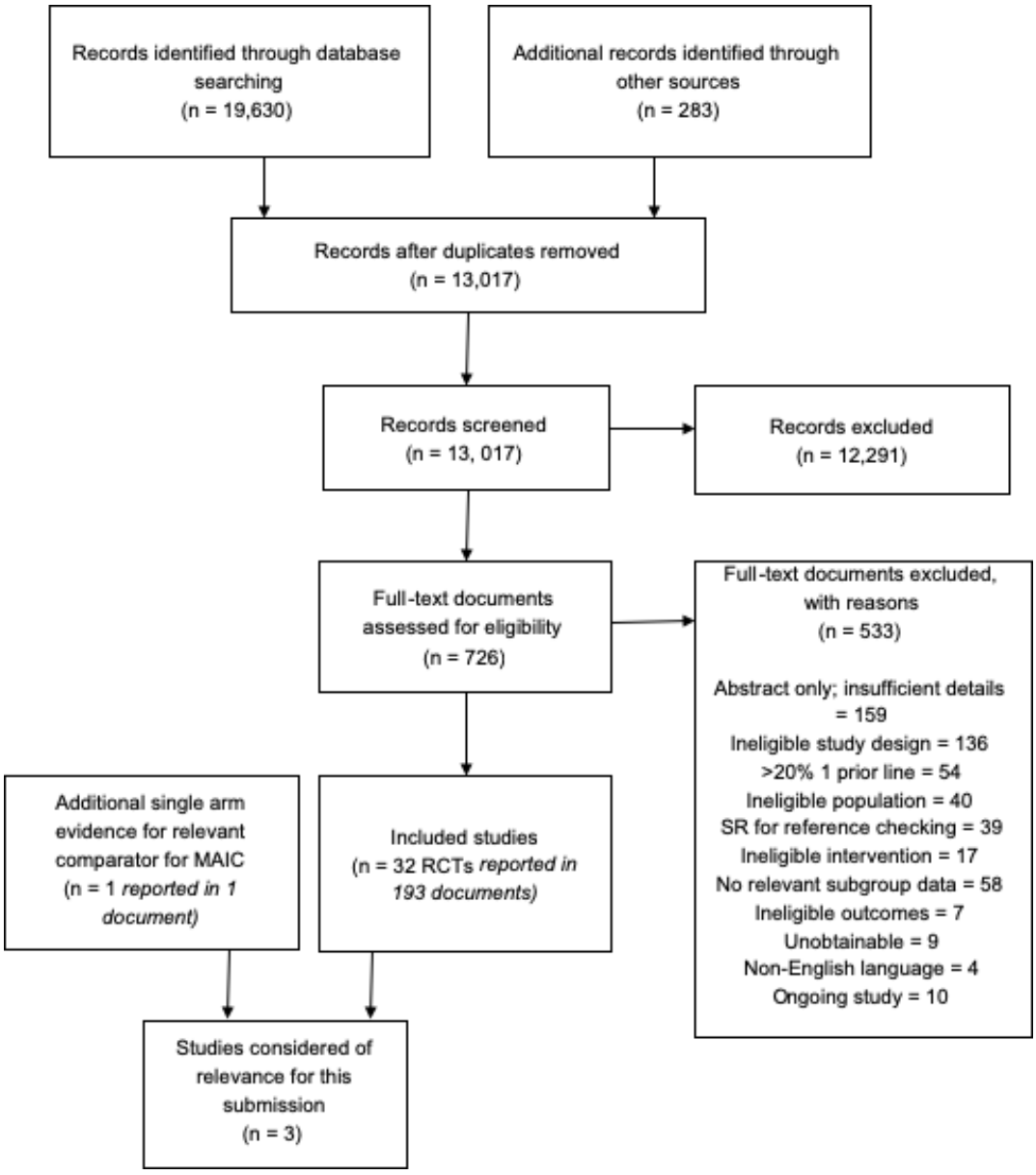
Figure 11 shows the PRISMA flow diagram of the numbers of records included and excluded at each stage of the selection process.

Following deduplication, 13,017 records remained for assessment; 12,291 records were excluded after an assessment of the information in the title and abstract and 726 full text documents were assessed. Overall, 32 studies (reported across 193 documents) met the eligibility criteria for the SLR (serving the global context with all the eligible comparators), of which 2 were deemed relevant for this submission. Due to the paucity of comparative data for the comparator PanVd a single arm trial was identified and included in the SLR and indirect treatment comparison (ITC) in this submission (see “Additional single arm evidence for relevant comparators for MAIC” in the PRISMA flow diagram).

A total of three studies were identified as relevant to this submission, one of which provides the direct evidence for IsaPD vs. Pd (ICARIA-MM) and the remaining two trials for PanVd inform the MAIC reported in Appendix K4.

A reference list of the included and excluded studies is provided in Appendix D (D.1.2.1).

Figure 11: PRISMA flow diagram of record selection process



Abbreviations: MAIC, matching-adjusted indirect comparison; RCT, randomised controlled trial; SR, systematic review

B.2.2 *List of relevant clinical effectiveness evidence*

The systematic review of clinical evidence identified a single phase III RCT including isatuximab (isatuximab in combination with pomalidomide plus a low dose of dexamethasone) as the population of interest to this submission (Table 4). An active comparator treatment (pomalidomide plus a low dose of dexamethasone) was used in the pivotal Phase III study EFC14335 (ICARIA-MM).

Table 4: List of relevant clinical evidence

Trial no. (acronym)	EFC14335 (ICARIA-MM)
Population	Adult patients (≥18 years old) with RRMM who have received at least two prior lines of therapy, including lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib, or ixazomib) alone or in combination, and have demonstrated disease progression on or within 60 days of completion of the last therapy
Intervention	**Experimental arm (n=154); Patients at 4L of treatment (n=52)**: • Isatuximab (SAR650984), 10 mg/kg IV infusion†, on Days 1, 8, 15, and 22 at Cycle 1, and then on Days 1 and 15 for subsequent cycles • Pomalidomide, 4 mg PO, on Days 1 to 21 of each 28-day cycle • Dexamethasone 40 mg (or 20 mg if the patient ≥75 years old) PO or IV, on Days 1, 8, 15 and 22 of each 28-day cycle
Comparator	**Active comparator arm (n=153), Patients at 4L of treatment (n=58):** • Pomalidomide, 4 mg PO, on Days 1 to 21 of each 28-day cycle • Dexamethasone 40 mg (or 20 mg if the patient ≥75 years old) PO or IV, on Days 1, 8, 15 and 22 of each 28-day cycle
Primary study ref(s)	CSR (44)
Refs identified but not used further	No other references identified
Is study excluded from further discussion? If yes state rationale	No (Pivotal Phase III study)

Abbreviations: CSR, clinical study report; IV, intravenous; MM, multiple myeloma; PO, oral; RRMM, relapsed and/or refractory multiple myeloma

Table 5: Clinical effectiveness evidence

Study	EFC14335 (ICARIA-MM) (interim report date: 4th April 2019)				
Study design	Phase III, prospective, open-label, multicentre, multinational, randomised, parallel group, double-arm study				
Population	Adult patients (≥18 years old) with RRMM who have received at least two prior lines of therapy, including lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib, or ixazomib) alone or in combination, and have demonstrated disease progression on or within 60 days of completion of the last therapy				
Intervention(s)	**Experimental arm (n=154); Patients in at 4L of treatment (n=52)** • Isatuximab (SAR650984), 10 mg/kg IV infusion†, on Days 1, 8, 15, and 22 at Cycle 1, and then on Days 1 and 15 for subsequent cycles • Pomalidomide, 4 mg PO, on Days 1 to 21 of each 28-day cycle • Dexamethasone 40 mg (or 20 mg if the patient ≥75 years old) PO or IV, on Days 1, 8, 15 and 22 of each 28-day cycle				
Comparator(s)	**Active comparator arm (n=153), Patients at 4L of treatment (n=58)** • Pomalidomide, 4 mg PO, on Days 1 to 21 of each 28-day cycle • Dexamethasone 40 mg (or 20 mg if the patient ≥75 years old) PO or IV, on Days 1, 8, 15 and 22 of each 28-day cycle				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale if trial not used in model	NA				
Reported outcomes specified in the decision problem	**Efficacy outcomes:** PFS, ORR, OS, TTP, HRQoL **Safety outcomes:** TEAEs (Grade 3–4; incidence ≥5%) up to 30 days after last study treatment administration				
All other reported outcomes	See Table 6				

Abbreviations: HRQoL, health-related quality of life; IV, intravenous; MM, multiple myeloma; NA, not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, oral; RRMM, relapsed and/or refractory multiple myeloma; TEAE, treatment-emergent adverse event; TTP, time to progression

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

B.2.3.1 *Summary of RCT methodology*

The methodology of the pivotal Phase III RCT ICARIA-MM is summarised in Table 6.

Table 6: Comparative summary of trial methodology

Trial number (acronym)	**EFC14335 (ICARIA-MM)**
Trial design	Phase III, prospective, open-label, multicentre, multinational, randomised, parallel group, double-arm study
Duration of study	10th January 2017–ongoing (cut-off date for efficacy analyses: 11th October 2018; cut-off date for other analysis [i.e. safety, disposition, demographics, and baseline characteristics]: 22nd November 2018) • Screening period: up to 21 days • Treatment period: 28-day cycles until disease progression, unacceptable AEs, patient preference or other reason of discontinuation • Follow-up period: patients who discontinued the study treatment due to disease progression were followed every 3 months for survival; patients who discontinued study treatment without disease progression were followed monthly until disease progression and every 3 months thereafter, for survival
Settings and locations where the data were collected	102 sites in 24 countries (Australia, Belgium, Canada, Czechia, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Korea, New Zealand, Norway, Poland, Portugal, Russia, Slovakia, Spain, Sweden, Taiwan, Turkey, UK, US)
Eligibility criteria for participants (extended information on eligibility criteria is presented in Table 7)	Adult patients (≥18 years old) with RRMM who have received at least two prior lines of therapy, including lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib, or ixazomib) alone or in combination, and have demonstrated disease progression on or within 60 days of completion of the last therapy
Method of randomisation	Eligible patients were randomly assigned, using an IRT system, in a 1:1 ratio to receive either isatuximab in combination with pomalidomide and dexamethasone (IsaPd – experimental arm) or pomalidomide with dexamethasone (Pd – control arm). Randomisation was stratified by: • Age (<75 years vs ≥75 years) • Number of previous lines of therapy (2 or 3 vs >3 lines)

Trial number (acronym)	EFC14335 (ICARIA-MM)
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])**	**Experimental arm: ITT population (n=154)/Patients at 4L of treatment (n=52)** • Isatuximab (SAR650984), 10 mg/kg IV infusion†, on Days 1, 8, 15, and 22 at Cycle 1, and then on Days 1 and 15 for subsequent cycles • Pomalidomide, 4 mg PO, on Days 1 to 21 of each 28-day cycle • Dexamethasone 40 mg (or 20 mg if the patient ≥75 years old) PO or IV, on Days 1, 8, 15 and 22 of each 28-day cycle **Active comparator arm: ITT population (n=153)/Patients at 4L of treatment (n=58)** • Pomalidomide, 4 mg PO, on Days 1 to 21 of each 28-day cycle • Dexamethasone 40 mg (or 20 mg if the patient ≥75 years old) PO or IV, on Days 1, 8, 15 and 22 of each 28-day cycle
Permitted concomitant medication	• Aspirin or another form of antithrombotic therapy (e.g. low-molecular weight heparin) • G-CSF prophylaxis (in patients with baseline extensive bone marrow involvement and/or low neutrophil count during the first three treatment cycles) • Palliative radiotherapy for pain management • Glucocorticoids, antihistamines, and analgesics, for the management of infusion reactions (IRs) • Prophylactic vaccination (influenza, pneumococcal and haemophilus influenza vaccines, as well as routine vaccines) to reduce the risk of infection
Disallowed concomitant medication	• Anti-myeloma therapies other than those specified in the study protocol • Systemic corticosteroids other than as part of the protocol-specified therapeutic regimen or for treatment of hypersensitivity reaction • Live vaccines • Strong CYP1A2 inhibitors, including cinafloxacin, ciprofloxacin, enoxacin, fluvoxamine, oltipraz, rofecoxib, and zafirlukast (consistent with the pomalidomide prescribing information)

Trial number (acronym)	EFC14335 (ICARIA-MM)
Key study objectives	**Primary objective:** • To demonstrate the benefit of IsaPd in the prolongation of PFS as compared with Pd in patients with RRMM **Secondary objective:** • To evaluate the ORR as per IMWG criteria in each study arm • To compare OS between the two study arms
Primary outcomes (including scoring methods and timings of assessments)	**Primary efficacy outcome:** • PFS from the date of randomisation to the date of first documentation of progressive disease[‡] or the date of death from any cause, whichever comes first
Other outcomes used in the economic model/specified in the scope	**Key secondary efficacy outcomes:** • ORR[§] from the date of randomisation to the date of first documentation of progressive disease[‡] • OS defined as the time from the date of randomisation to date of death from any cause **Other secondary efficacy outcomes:** • TTP from the date of randomisation to the date of first documentation of progressive disease[‡] • HRQoL assessed by means of the electronic questionnaires EORTC-QLQ-C30, EORTC-QLQ-MY20 and EQ-5D-5L, completed by patients at the centre prior to study-related activities on Day 1 of each treatment cycle, at the end of treatment (EOT)[††] visit, and 60 days (±5 days) after last study treatment administration **Safety outcomes:** • TEAEs (grade 3–4[‡‡]; incidence ≥5%) up to 30 days after last study treatment administration

Trial number (acronym)	EFC14335 (ICARIA-MM)
Pre-planned subgroups	Results for the primary endpoint (PFS) were analysed by the following subgroups: • Age: <65 years, 65–74, ≥75 years • Number of previous lines of therapy:2 or 3 prior lines, >3 prior lines • Gender: male, female • Race: Caucasian, Asian, other • Geographical region: Western Europe, Eastern Europe, North America, Asia, other countries • Regulatory region: Western countries, other countries • Eastern Cooperative Oncology Group (ECOG) performance status[§§] at baseline: 0, 1, 2 • R-ISS/ISS staging at study entry: I, II, III • Cytogenetic abnormality (del(17p), t(4;14), t(14;16)): ≥1, none • Cytogenetic abnormality del(17p): Yes, No • MM subtype at diagnosis: IgG, non-IgG • Baseline creatinine clearance (MDRD formula): ≥60 ml/min/1.73 m^2, <60 ml/min/1.73 m^2 • Refractory to proteasome inhibitor: Yes, No • Refractory to lenalidomide: Yes, No

†First infusion initiated at 175 mg/h and, in the absence of IRs after 1 hour of infusion, increased by 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h. Subsequent infusions initiated at 175 mg/h and, in the absence of IRs after 1 hour of infusion, increased by 100 mg/h increments every 30 minutes, to a maximum of 400 mg/h. ‡As defined by the IRC. §Defined as the proportion of patients with stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR) as best overall response (BOR) and assessed by the IRC using the IMWG criteria. ¶Defined as PFS in the subgroup of patients carrying high risk cytogenetic abnormalities, namely del(17p), t(4;14) or t(14;16) assessed by fluorescence *in situ* hybridisation (FISH). †† Time defined as 30 days after last study treatment administration. ‡‡According to the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 grade scaling. §§ECOG performance status (66): Grade 0–5, with 'Grade 0' meaning that the patient is fully active/able to carry on all pre-disease performance without restrictions, and 'Grade 5' meaning that the patient is dead.

Abbreviations: BOR, best overall response; CR, complete response; ECOG, Eastern Cooperative Oncology Group; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire with 30 items; EORTC-QLQ-MY20, European Organisation for Research and Treatment of Cancer Quality of Life Multiple Myeloma Specific Module with 20 items; EOT, end of treatment; EQ-5D-5L, Euro QoL Group self-report questionnaire with 5 dimensions and 5 levels per dimension; FISH, fluorescence in situ hybridisation; G-CSF, granulocyte-colony stimulating factor; IMWG, International Myeloma Working Group; IRC, Independent Response Committee; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ISS, International Staging System; MDRD, Modification of Diet in Renal Disease; MM, multiple myeloma; NCI-CTCAE, National Cancer Institute - Common Terminology Criteria for Adverse Events version 4.03 grade scaling ORR, overall response rate; OS, overall survival; Pd, pomalidomide, low-dose dexamethasone; PFS, progression free survival; PR, partial response; PS, performance status; sCR, stringent complete response; VGPR, very good partial response; TEAEs, treatment-emergent adverse events; TTP, time to progression

Table 7: Extended eligibility criteria for RTCs

Trial number (acronym)	EFC14335 (ICARIA-MM)

Inclusion criteria	• Patients aged ≥18 with documented diagnosis of MM with evidence of measurable disease:
	  ○ Serum M protein ≥0.5 g/dL (measured using serum protein immunoelectrophoresis) and/or
	  ○ Urine M protein ≥200 mg/24 hours (measured using urine protein immunoelectrophoresis)
	• Patients who have received at least two prior lines of anti-myeloma therapy, including at least two consecutives cycles of lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) given alone or in combination
	• Patients who have failed treatment with lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) alone or in combination, defined by any of the following:
	  ○ Progression had occurred while on or within 60 days from end of the treatment with lenalidomide and/or a proteasome inhibitor
	  ○ In case of previous response to lenalidomide and/or a proteasome inhibitor, patient had progressed within 6 months after discontinuation of the treatment
	  ○ Patients who had developed intolerable toxicity[†] after a minimum of two consecutive cycles of a regimen containing lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) alone or in combination
	• Patients who have progressed on or within 60 days after end of the previous therapy before study entry (i.e. refractory to the previous line of treatment), including the following two categories:
	  ○ Refractory disease: patients who were refractory to all previous lines of treatment but had achieved at least a minimal response (MR) in one previous line
	  ○ Relapsed and refractory disease: patients who were relapsed from at least one previous line of treatment and refractory to the last line of treatment. Patients could have been refractory to other previous line/lines of treatment
	• Patients who were willing/able to give written informed consent before taking part in any study-related procedures (apart from normal medical care) with the understanding that their consent could have been withdrawn at any time without prejudice to their medical care

Exclusion criteria	• Primary refractory multiple myeloma defined as patients who have never achieved at least a minimal response (MR) with any treatment during the disease course • Free Light Chain (FLC) measurable disease only • Patient previously treated with anti-CD38 monoclonal antibody, with progression on or within 60 days after end of anti-CD38 monoclonal antibody treatment or failure to achieve at least MR to treatment (i.e., refractory to anti-CD38) • Prior therapy with pomalidomide

Trial number (acronym)	EFC14335 (ICARIA-MM)
	• Any anti-myeloma drug treatment (including dexamethasone) within 14 days before randomisation • Prior allogenic hematopoietic stem cell (HSC) transplant with active graft vs host disease (GvHD) any grade and/or were under immunosuppressive treatment within the last 2 months • Any major procedure within 14 days before the initiation of the study treatment: plasmapheresis, major surgery (kyphoplasty was not considered a major procedure), radiotherapy • Patient who had received any other investigational drugs or prohibited therapy for this study within 28 days or five half-lives from randomisation, whichever was longer • ECOG performance status >2 • Platelets <75 000 cells/μL if <50% of bone marrow (BM) nucleated cells are plasma cells, and <30 000 cells/μL if ≥50% of BM nucleated cells are plasma cells (platelet transfusion not allowed within three days before the screening visit) • Absolute neutrophils count (ANC) <1000/μL (1 x 10^9/L) (use of G-CSF not allowed to reach this level) • Creatinine clearance <30 mL/min (MDRD Formula) • Total bilirubin >2 x upper limit of normal (ULN) • Corrected serum calcium >14 mg/dL (>3.5 mmol/L) • Aspartate aminotransferase (AST) and/or Alanine Aminotransferase (ALT) >3 x ULN • Ongoing toxicity (excluding alopecia and those listed in eligibility criteria) from any prior anti-myeloma therapy >Grade 1[‡] • Hypersensitivity to IMiDs (thalidomide or lenalidomide) defined as any hypersensitivity reaction leading to stop IMiDs within the first two cycles or a reaction which does meet intolerance definition[†] • Hypersensitivity to dexamethasone, sucrose histidine (as base and hydrochloride salt), and polysorbate 80 or any of the components of study therapy that are not amenable to premedication with steroids, or H2 blockers that would disallow further treatment with these agents • Significant cardiac dysfunction; myocardial infarction within 12 months; unstable, poorly controlled angina pectoris • Diagnosed or treated for another malignancy within 3 years prior to randomisation with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an *in-situ* malignancy, or low risk prostate cancer after curative therapy • Patients positive for human immunodeficiency virus (HIV) or with hepatitis A, B or C active infection • Malabsorption syndrome or any condition that could have significantly impacted the absorption of pomalidomide • Active primary amyloid-light (AL) amyloidosis (evidence of end organ damage or receiving treatment for amyloidosis)

Trial number (acronym)	EFC14335 (ICARIA-MM)
	• Concomitant plasma cell leukaemia • Unable or unwilling to undergo thromboprophylaxis • Daily requirement for corticosteroids (equivalent to ≥10 mg/day of prednisone) for >7 days (except for inhalation corticosteroids) • Pregnant or breastfeeding woman or female who intends to become pregnant during the participation in the study • Male participants who disagree to practice true abstinence or disagree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and at least 3 months following study treatment discontinuation, even if he has undergone a successful vasectomy • All patients who disagree to refrain from donating blood while on study treatment and for 4 weeks after discontinuation from this study treatment • All patients who did not agree to keep study treatment for their personal use only • Any country-related specific regulation that prevented the patient from entering the study • Any severe acute or chronic medical condition which would have impaired the ability of the patient to participate in the study or interfered with interpretation of study results (e.g. systemic infection unless specific anti-infective therapy was employed) or patient's inability to comply with the study procedures

† Intolerance defined: for proteasome inhibitor containing regimens, as any toxicity leading to discontinuation of a proteasome inhibitor (e.g. ≥Grade 2 peripheral neuropathy or ≥Grade 2 neuropathic pain. Peripheral neuropathy must have been ≤Grade 1 before study entry [according to NCI-CTCAE v4.03]); for lenalidomide containing regimens, as any toxicity leading to discontinuation of lenalidomide (e.g. Grade 3 rash. Rash could not have been Grade 4, and other non-hematologic toxicities could not have been Grade 4. All non-hematologic toxicities had to be ≤Grade 1 before study entry). ‡According to NCI-CTCAE version 4.03 grade scaling
Abbreviations: AL, amyloid-light; ALT, alanine aminotransferase; ANC, absolute neutrophils count; AST, aspartate aminotransferase; BM, bone marrow; CD38, cluster of differentiation 38; ECOG, Eastern Cooperative Oncology Group; FLC, Free Light Chain; G-CSF, granulocyte-colony stimulating factor; GvHD, graft vs host disease; HIV, human immunodeficiency virus; HSC, hematopoietic stem cell; IMiDs, immunomodulatory drugs; MDRD, Modification of Diet in Renal Disease; MM, multiple myeloma; MR, minimal response; ULN, upper limit of normal.

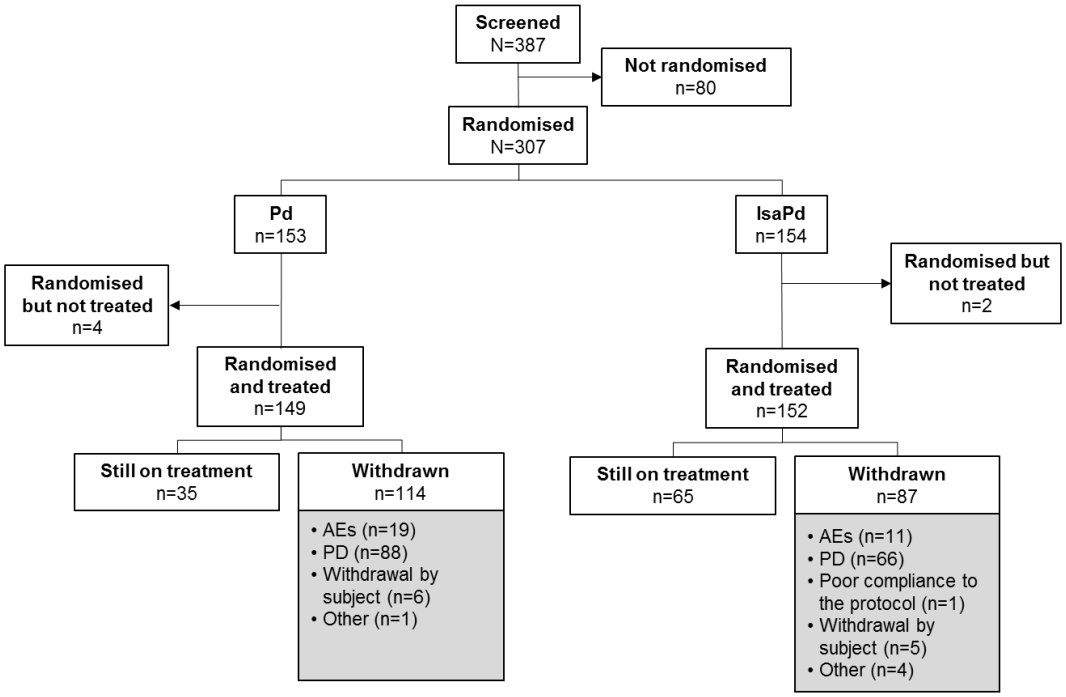
B.2.3.1.1 Patient disposition

A total of 387 patients were screened and 307 patients were randomly assigned to either the IsaPd arm (n=154) or the Pd arm (n=153). Six of the 307 randomised patients (4 patients in the Pd and 2 patients in the IsaPd) were withdrawn before receiving study medication, 3 due to AEs (pre-existing thrombocytopenia in 2 patients and hyperviscosity in 1 patient), 1 due disease progression, 1 who withdrew consent, and 1 patient, a woman of childbearing potential (WOCBP), who showed unwillingness to prevent pregnancy or to be tested for pregnancy.

Overall, as of the data cut-off date, nearly twice as many patients in the IsaPd arm (42.2%) than in the Pd arm (22.9%) were still on treatment. The proportion of patients who withdrew from the study was higher in the Pd group than in the IsaPd group (74.5% vs 56.5%); the most common reason for withdrawal was progressive disease (57.5% and 42.9% in the Pd and IsaPd groups, respectively), followed by AEs (12.4% and 7.1% in the Pd and IsaPd groups, respectively).

A CONSORT diagram for ICARIA-MM is presented in **Figure 12**.

Figure 12: CONSORT diagram for ICARIA-MM



Abbreviations: AEs, adverse events; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; Pd, pomalidomide, low-dose dexamethasone; PD, progressive disease.

B.2.3.1.2 Patient demographics and baseline characteristics

ICARIA-MM – ITT population

Patient demographics at baseline were generally similar between the two treatment arms, with exception of geographic region and gender (Table 8). Overall, the mean age of patients was 66.6 years and 65.2 years in the IsaPd arm and in the Pd arm

respectively. Although the two treatment arms were similar in terms of age stratification factor, there were more patients ≥65 years in the IsaPd arm than in the Pd arm (64.9% vs 54.2%), with the majority of patients showing a baseline ECOG PS score ≤1 (89.6%). Nearly half (51.8%) of the ICARIA-MM population was male, although the proportion of males was higher in the IsaPd arm than in the Pd arm (57.8% vs 45.8%). Most patients were White (79.5%), with fewer patients from Western Europe in the IsaPd arm compared with the Pd arm (35.7% vs 49.7%) and more patients from Eastern Europe (18.2% vs 13.1%) and Asia (13.6% vs 9.8%).

Baseline disease-specific characteristics were as expected in this heavily-treated RRMM population and similar between the two treatments arms (Table 9). Most patients in both treatment groups had MM subtype IgG (66.8%), and ISS Stage I and II (73%). A total of 36.2% had impaired renal function (<60 mL/min/1.73m^2) at baseline, with a slightly higher proportion recorded in IsaPd arm (IsaPd 38.7% vs Pd 33.8%). All patients (100%) were considered “relapsed and refractory”, with 92.5% refractory to lenalidomide and 75.9% to proteasome inhibitor. Overall, 19.5% of patients had high-risk chromosomal abnormalities (CA) with del(17p) and t(4;14) being the most frequent abnormalities. The percentage of patients with high-risk CA was lower in the IsaPd arm compared with the Pd arm (15.6% vs 23.5%). Eight (2.6%) patients (3 in the IsaPd arm and 5 in Pd arm) had two high-risk CA. The overall mean number of prior lines was 3.42, with 104 (33.9%) patients having received 4 or more prior lines of treatment.

ICARIA-MM – Patients at 4L of treatment

Patient demographics at baseline for 4L patients were generally aligned with those of the overall population and comparable between the two treatment arms (Table 8). Overall, the mean age of patients was 66.1 years and 64.2 years in the IsaPd arm and in the Pd arm respectively. Although the two treatment arms were similar in terms of age stratification factor, there were more patients ≥65 years in the IsaPd arm than in the Pd arm (63.5% vs 53.4%), with the majority of patients showing a baseline ECOG PS score ≤1 (90.0%). Nearly half (51.8%) of the ICARIA-MM population was male, although the proportion of males was higher in the IsaPd arm than in the Pd arm (57.7% vs 46.6%). Most patients were White (84.5%), with fewer patients from Western Europe in the IsaPd arm compared with the Pd arm (36.5% vs 50.0%) and more patients from Eastern Europe (25.0% vs 17.2%) and North America (5.8% vs 0.0%).

Baseline disease-specific characteristics were as expected in this heavily-treated RRMM population and similar between the two treatments arms (Table 9). Most patients in both treatment groups had MM subtype IgG (61%), and ISS Stage I and II (73%). A total of 39% had impaired renal function (<60 mL/min/1.73m2) at baseline, with a slightly higher proportion recorded in Pd arm (IsaPd 37.5% vs Pd 40.4%) All patients (100%) were considered “relapsed and refractory”, with 90% refractory to lenalidomide and 73% to proteasome inhibitor. Overall, 19% of patients had high-risk chromosomal abnormalities (CA) with del(17p) and t(4;14) being the most frequent abnormalities. The percentage of patients with high-risk CA was lower in the IsaPd arm compared with the Pd arm (15.4% vs 22.4%). Four (3.6%) patients (1 in the IsaPd arm and 3 in the Pd arm) had two high-risk CA.

Table 8: Baseline demographics of patients in ICARIA-MM trial (randomised population)

Baseline demographics	ICARIA-MM – ITT population		ICARIA_MM – Patients in 4L	
	Pd (N=153)	IsaPd (N=154)	Pd (N=58)	IsaPd (N=52)
Age, years, mean (SD)	65.2 (9.5)	66.6 (9.1)	64.2 (8.9)	66.1 (8.5)
Age group, years, n (%)				
<65	70 (45.8)	54 (35.1)	27 (46.6)	19 (36.5)
65–74	54 (35.3)	68 (44.2)	22 (37.9)	26 (50.0)
≥75	29 (19.0)	32 (20.8)	9 (15.5)	7 (13.5)
Sex, n (%)				
Male	70 (45.8)	89 (57.8)	27 (46.6)	30 (57.7)
Female	83 (54.2)	65 (42.2)	31 (53.4)	22 (42.3)
Race, n (%)				
White	126 (82.4)	118 (76.6)	51 (87.9)	42 (80.8)
Black or African American	3 (2.0)	1 (0.6)	1 (1.7)	0
Asian	15 (9.8)	21 (13.6)	5 (8.6)	5 (9.6)
Native Hawaiian or other Pacific Islander	1 (0.7)	2 (1.3)	0	2 (3.8)
Missing/Not reported	8 (5.2)	12 (7.8)	1 (1.7)	3 (5.8)
Ethnicity, n (%)				
Hispanic or Latino	3 (2.0)	4 (2.6)	1 (1.7)	3 (5.8)
Not Hispanic or Latino	134 (87.6)	130 (84.4)	51 (87.9)	42 (80.8)

Baseline demographics	ICARIA-MM – ITT population		ICARIA_MM – Patients in 4L	
	Pd (N=153)	IsaPd (N=154)	Pd (N=58)	IsaPd (N=52)
ECOG PS, n (%)				
0	69 (45.1)	55 (35.7)		21 (40.4)
1	68 (44.4)	83 (53.9)	23 (39.7)	25 (48.1)
2	16 (10.5)	16 (10.4)	5 (8.6)	6 (11.5)
Geographical region, n (%)				
Western Europe	76 (49.7)	55 (35.7)	29 (50.0)	19 (36.5)
Eastern Europe	20 (13.1)	28 (18.2)	10 (17.2)	13 (25.0)
North America	5 (3.3)	7 (4.5)	0	3 (5.8)
Asia	15 (9.8)	21 (13.6)	5 (8.6)	5 (9.6)
Other countries†	37 (24.2)	43 (27.9)	14 (24.1)	12 (23.1)
Regulatory region, n (%)				
Western countries	97 (63.4)	77 (50.0)	33 (56.9)	27 (51.9)
Other countries‡	56 (36.6)	77 (50.0)	25 (43.1)	25 (48.1)

†Other countries: Australia, New Zealand, Turkey and Russia. ‡ Other countries: Czechia, Hungary, Poland, Slovakia, Japan, Korea, Taiwan, Turkey and Russia.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; N/n, number of patients; Pd, pomalidomide, low-dose dexamethasone; SD, standard deviation.

Table 9: Baseline disease-specific characteristics of patients in ICARIA-MM trial (randomised population)

Baseline characteristics	ICARIA-MM – ITT population		ICARIA_MM – Patients in 4L	
	Pd (N=153)	IsaPd (N=154)	Pd (N=58)	IsaPd (N=52)
MM subtype, n (%)				
IgG	101 (66.0)	104 (67.5)	36 (62.1)	31 (59.6)
Non-IgG	52 (34.0)	50 (32.5)	22 (38.0)	21 (40.4)
Biclonal status, n (%)				
Yes	2 (1.3)	1 (0.6)	2 (3.4)	0
Beta 2-microglobulin† (mg/L)				
Mean (SD)	5.71 (6.72)	4.68 (3.84)	6.93 (9.44)	4.17 (2.90)
<3.5, n (%)	65 (43.3)	77 (51.0)	27 (47.4)	30 (58.8)
3.5–5.4, n (%)	42 (28.0)	40 (26.5)	11 (19.3)	12 (23.5)
≥5.5, n (%)	43 (28.7)	34 (22.5)	19 (33.3)	9 (17.6)
Albumin (g/L)				
Mean (SD)	36.93 (5.49)	36.81 (5.36)	37.71 (5.47)	38.06 (5.06)
<35, n (%)	48 (31.4)	52 (33.8)	14 (24.1)	12 (23.1)
≥35, n (%)	48 (31.4)	52 (33.8)	44 (75.9)	40 (76.9)
Serum LDH, n (%)				
≤ULN	102 (66.7)	106 (68.8)	35 (60.3)	36 (69.2)
ISS stage, n (%)				
Stage I	51 (33.3)	64 (41.6)	24 (41.4)	25 (48.1)
Stage II	56 (36.6)	53 (34.4)	14 (24.1)	17 (32.7)
Stage III	43 (28.1)	34 (22.1)	19 (32.8)	9 (17.3)

Baseline characteristics	ICARIA-MM – ITT population		ICARIA_MM – Patients in 4L	
	Pd (N=153)	IsaPd (N=154)	Pd (N=58)	IsaPd (N=52)
R-ISS stage, n (%)				
Stage I	31 (20.3)	39 (25.3)	13 (22.4)	15 (28.8)
Stage II	98 (64.1)	99 (64.3)	34 (58.6)	31 (59.6)
Stage III	24 (15.7)	16 (10.4)	11 (19.0)	6 (11.5)
Refractory status, n (%)				
Relapsed and refractory[‡]	153 (100)	154 (100)	58 (100)	52 (100)
Refractory to lenalidomide	140 (91.5)	144 (93.5)	51 (87.9)	48 (92.3)
Refractory to PI	115 (75.2)	118 (76.6)	40 (69.0)	40 (76.9)
Number of prior lines				
2 or 3	103 (67.3)	97 (63.0)	—	—
>3	50 (32.7)	57 (37.0)	58 (100)	52 (100)
Cytogenetic risk, n (%)				
High-risk CA[§]	36 (23.5)	24 (15.6)	13 (22.4)	8 (15.4)
del(17p)[¶]	23 (15.0)	14 (9.1)	10 (17.2)	5 (9.6)
t(4;14)[¶]	14 (9.2)	12 (7.8)	6 (10.3)	4 (7.7)
del(17p) and t(4;14) [††]	4 (2.6)	3 (1.9)	3 (5.2)	1 (1.9)
del(17p) and t(14;16) [††]	1 (0.7)	0	0	0
Creatinine clearance (MDRD), n (%)				
≥60 mL/min/1.73m^2	96/145 (66.2%)	87/142 (61.3%)	34/57 (59.6)	30/48 (62.5)
<60 mL/min/1.73m^2[‡‡]	49/145 (33.8%)	55/142 (38.7%)	23/57 (40.4)	18/48 (37.5)

†Pd: N=150; IsaPd: N=151. ‡Excluding primary refractory. §High risk CA is defined as the presence of del(17p) and /or translocation t(4;14) and /or translocation t(14;16). ¶ Abnormality considered positive if present in at least 30% of analysed plasma cells, except for del(17p) where the threshold is at least 50%. ††High-risk cytogenetic abnormalities ‡‡Renal function impairment defined as creatinine clearance (MDRD) <60 mL/min/1.73m^2.
Abbreviations: CA, chromosomal abnormalities; Ig, Immunoglobulin; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; MDRD, Modification of Diet in Renal Disease; N/n, number of patients; Pd, pomalidomide, low-dose dexamethasone; PI, proteasome inhibitor; SD, standard deviation; R-ISS: Revised International Staging System; ULN, upper limit of normal.

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

A CONSORT diagram (Figure 12) showing the flow of participants through each stage of each of the ICARIA-MM trial is also, provides details of the numbers of eligible participants, and on the number of participants randomised and allocated to each treatment.

B.2.4.1 *Populations analysed*

Definitions of the populations analysed in ICARIA-MM are listed below:

- **Intent-to-treat (ITT) population:** included all randomised patients with a signed informed consent, regardless of whether the patient was treated or not. The ITT population was used for all efficacy analyses and patients were analysed according to the treatment group they were originally allocated to. No patients were randomised into a group and received another study treatment.
- **Safety population:** included all patients from the ITT population subjects who received at least one dose or part of the dose of randomised treatment. The safety population was used for all safety data analysis and patients were analysed according to the treatment group they were originally allocated to.

B.2.4.2 *Statistical information*

A summary of the statistical methods used in ICARIA-MM is presented in Table 10.

Table 10: Summary of statistical analyses in ICARIA-MM

Trial number (acronym)	EFC14335 (ICARIA-MM)
Hypothesis objective	To demonstrate the benefit of IsaPd in the prolongation of PFS as compared with Pd in patients with RRMM
Statistical analysis of primary efficacy endpoint	• **Primary efficacy analysis:** o The primary endpoint, PFS, was analysed using the Kaplan-Meier method by treatment arm (IsaPd and Pd) and compared by means of a log-rank test, stratified by the randomisation factors as entered into the IRT (i.e. age and number of previous lines of therapy) and using a 1-sided 0.025 alpha level. The critical value for the Wald test hazard ratio (HR) scale was 0.734 • **Sensitivity analyse**s were conducted at a 1-sided 0.025 alpha level to assess the robustness of the primary analysis. The same statistical methods used in the primary analysis were applied to the PFS data but using different censoring and event rules; these analyses included: o PFS analysis without censoring for further anti-myeloma treatment o PFS analysis using investigator assessment of response (based on local laboratory M-protein laboratory results and local radiology results) o PFS analysis using Investigator's disease assessment, including symptomatic deterioration (clinical progression with no progression on imaging or M-protein per Investigator) as an event o Initiation of further anti-myeloma treatment considered as a PFS event

Trial number (acronym)	EFC14335 (ICARIA-MM)
	○ Analysis based on scheduled assessment dates instead of actual assessment dates and late PFS censored (analysis done if lack of adherence to the protocol-defined schedule of disease assessments between the treatment groups has been detected) • **Subgroup analyses** were conducted for evaluation of consistency of the results from the primary analysis. For each subgroup, the treatment effect HR and its associated 95% CI was estimated. For each predefined demographic/baseline factor, PFS was analysed using a Cox proportional hazards model with terms for the factor, treatment and their interaction. The test of the interaction was performed at the 10% alpha level • **Multivariate analyses** were conducted to evaluate the potential impact of confounding factors in the results from the primary analysis. A multivariate Cox proportional hazards model was used to identify prognostic factors among the demographic and baseline characteristics factors described in the, using a stepwise selection procedure with a 15% significance level for removing effects. For significant prognostic factors identified in the multivariate model, the balance between treatment groups was assessed. When a major confounding factor was identified for treatment group imbalances in a prognostic factor at baseline, an exploratory analysis of PFS was done after adjusting for the prognostic factors in the multivariate Cox proportional hazards model
Statistical analysis of secondary efficacy endpoints	**ORR, BOR, and CBR** (**based on IRC and Investigator assessments)** • These efficacy variables were summarised for the ITT population with descriptive statistics • Confidence intervals were computed using the Clopper-Pearson method • ORR and proportion of patients with BOR ≥VGPR (based on IRC assessment) were compared between treatment groups using a Cochran-Mantel-Haenszel test stratified by factors as entered in the IRT **OS** • The analysis of OS consisted of a comparison between treatment groups through a 1-sided log-rank test stratified by factors as entered in the IRT • O'Brien and Fleming α spending function was used to obtain the nominal significance levels for the interim and final analyses of survival • A sensitivity analysis was performed where OS was adjusted for switching to daratumumab as a subsequent treatment using inverse probability of censoring weighting (IPCW) method **TTP, DOR, TTFR, and TTBR (based on IRC assessments)** • These time-to-event variables were analysed using Kaplan-Meier methods **MRD** • The MRD status was summarised by treatment group in the ITT population using descriptive statistics **PROs** • Descriptive analyses of PROs were performed for the Safety population evaluable for C30, MY20 and EQ-5D-5L
Statistical analysis of safety endpoints	The analysis of the safety variables was descriptive, and no systematic testing was performed
Sample size, power calculation	The sample size calculation was based on the primary efficacy endpoint (PFS), using the following assumptions:

Trial number (acronym)	EFC14335 (ICARIA-MM)
	• Pd arm had a median PFS of 4.0 months • IsaPd arm had 40% risk reduction in hazard rate in comparison to Pd arm; the targeted HR was 0.60, which corresponded to an improvement in the true median PFS time from 4 months to 6.67 months • A log-rank test at a 1-sided significance level of 2.5% Based on the above assumptions, a total of **162 PFS events were required to achieve a 90% power for the study** The key secondary endpoint, OS, also contributed to determine the sample size, using the following assumptions: • Pd arm had a median OS of 13.0 • IsaPd had a 31.5% risk reduction in HR in comparison with Pd arm; the targeted HR was 0.685 and this was expected to correspond to a difference of 6 months in median OS between the control arm and the experimental arm • A log-rank test at a 1-sided significance level of 2.5% • An interim analysis for OS was planned at the time of primary analysis of PFS, which was estimated (at the time of protocol development) to occur when about 36% of the OS events were observed. An O'Brien and Fleming α-spending function was used to obtain the nominal significance levels for the interim (according to the actual number of events) and final analyses of survival Based on the above assumptions, a total of **220 deaths were required to achieve 80% power for the study** Approximately **300 patients (150 in each arm)** were expected to be adequate to achieve the targeted number of events for both PFS and OS
Data management and patient withdrawals	**Data management** • ICARIA-MM is an ongoing study. Interim data as per cut-off date of 11th October 2018, for efficacy analysis, and 22nd November 2018, for other analysis (i.e. safety, disposition, demographics, and baseline characteristics), are reported • Data entry and validation were carried out using standard validated remote data capture computer software (RAVE version 2018.1.3). Data were stored in a SQL server database • Data entry was performed directly from the Investigator site from the data source documents and signed electronically by the authorised site personnel. Moreover, any modification in the database was traced using an audit trail **Data management for patient withdrawals in primary analysis** • Patients without PD or death before the analysis cut-off or the date of initiation of further anti-myeloma treatment were censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever came first • Patients with no PFS events (death or PD) and without any valid post baseline disease assessments were censored at the day of randomisation (Day 1)

Abbreviations: BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; DOR, duration of response; HR, hazard ratio; IPCW, inverse probability of censoring weighting; IRC, independent response committee; IRT, interactive response technology; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ITT, intention-to-treat; MRD, minimal residual disease; ORR, overall response rate; OS,

overall survival; Pd, pomalidomide, low-dose dexamethasone; PD, progressive disease; PFS, progression free survival; TTBR, time to best response; TTFR, time to first response; TTP, time to progression.

B.2.5 *Quality assessment of the relevant clinical effectiveness evidence*

Please see Appendix K.4.3 for a quality assessment of ICARIA-MM.

B.2.6 *Clinical effectiveness results of the relevant trials*

B.2.6.1 *Study EFC14335 (ICARIA-MM)*

B.2.6.1.1 Primary efficacy outcome: PFS as per cut-off date 11th October 2018

ICARIA-MM – ITT population

The efficacy results for the primary analysis of PFS in the ICARIA-MM trial, are presented in Table 11 and Figure 13. In the ITT population for the study, the addition of isatuximab to pomalidomide and low dose dexamethasone significantly improved PFS (one-sided p=0.001, meeting the pre-specified efficacy boundary of 0.025) vs pomalidomide and low dose dexamethasone alone. Median PFS was significantly prolonged in the IsaPd arm (11.53 months [95% CI; 8.936, 13.897]) in comparison with the Pd arm (6.47 months [95% CI; 4.468, 8.279]). The stratified HR was 0.596 (95% CI; 0.436, 0.814) representing a 40.4% risk reduction of disease progression or death in favour of IsaPd vs Pd, which is consistent with the hypothesised HR of 0.6 (see 'sample size, power calculation' in Table 10).

In the ICARIA trial, participants were censored when information on time-to-event was not available due to non-occurrence of the event before the end-of-trial. At the cut-off date, a total of 81 (52.6%) and 64 (41.8%) patients in the IsaPd and Pd arms, respectively, had not had a PFS event and were censored. This means that, for the analysis of PFS in the overall population, data were available for only 47−58% of patients.

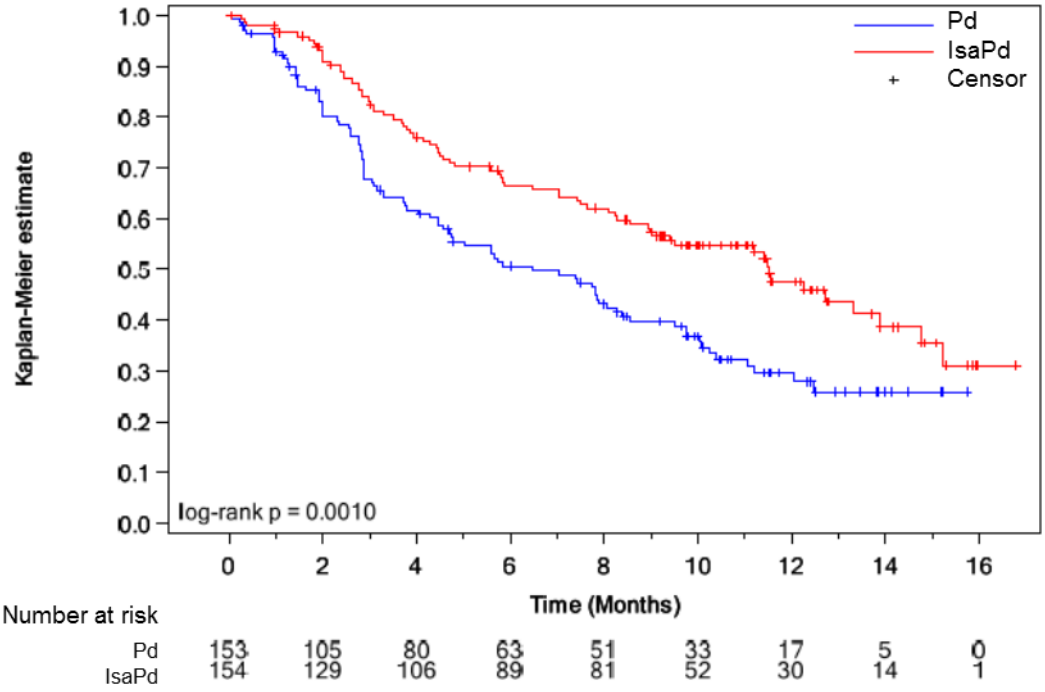
Table 11: ICARIA-MM primary efficacy outcome – PFS[†] (ITT population)

	Pd (N=153)	**IsaPd (N=154)**
Number (%) of events	89 (58.2)	73 (47.4)
Number (%) of patients censored	64 (41.8)	81 (52.6)
Kaplan-Meier estimates of PFS in months		
25% quantile (95% CI)	2.76 (1.971; 3.055)	4.27 (3.088; 5.848)
Median (95% CI)	6.47 (4.468; 8.279)	11.53 (8.936; 13.897)
75% quantile (95% CI)	NC (10.382; NC)	NC (14.784; NC)
Stratified[‡] Log-Rank test p-value[§] vs Pd	0.0010	
Stratified[‡] HR[¶] (95% CI) vs Pd	0.596 (0.436; 0.814)	
PFS probability (95% CI)[††]		

	Pd (N=153)	IsaPd (N=154)
2 months	0.801 (0.723; 0.859)	0.910 (0.850; 0.947)
4 months	0.617 (0.529; 0.694)	0.760 (0.681; 0.822)
6 months	0.506 (0.417; 0.588)	0.665 (0.580; 0.737)
8 months	0.432 (0.345; 0.516)	0.620 (0.534; 0.695)
10 months	0.369 (0.284; 0.453)	0.547 (0.459; 0.627)
12 months	0.296 (0.213; 0.384)	0.476 (0.380; 0.566)
14 months	0.259 (0.174; 0.351)	0.387 (0.277; 0.495)
16 months	0.259 (0.174; 0.351)	0.310 (0.186; 0.443)
Number of patients at risk††		
2 months	105	129
4 months	80	106
6 months	63	89
8 months	51	81
10 months	33	52
12 months	17	30
14 Months	5	14
16 Months	0	1

†As per cut-off date: 11th October 2018. ‡Stratified by age (<75 years vs ≥75 years) and number of previous lines of therapy (2 or 3 vs >3) according to IRT. §One-sided significance level: 0.025. ¶HR<1 favours IsaPd arm. ††Estimated using the Kaplan-Meier method.
Abbreviations: CI, confidence interval; NC, not calculable; HR, hazard ratio; IRT, interactive response technology; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ITT, intention-to-treat; MM, multiple myeloma; Pd, pomalidomide, low-dose dexamethasone; PFS, progression free survival.

Figure 13: ICARIA-MM primary endpoint – PFS† – Kaplan-Meier curves by treatment group (ITT population)



†Cut-off date: 11th October 2018.
Log-rank p-value stratified by age (<75 years vs ≥75 years) and number of previous lines of therapy (2 or 3 vs >3) according to IRT. One-sided significance level: 0.025.
Abbreviations: IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; IRT, interactive response technology; ITT, intention-to-treat; MM, multiple myeloma; Pd, pomalidomide, low-dose dexamethasone; PFS, progression free survival.

Sensitivity analysis of the primary outcome

The overall results for the sensitivity analyses conducted were consistent with those of the primary analysis for PFS. The analysis showed HR values ranging from 0.568 to 0.602, and the median PFS values ranging from 8.97 to 11.53 months in the IsaPd arm, and from 4.60 to 6.47 months in Pd arm, demonstrating a statistically significant difference in favour of IsaPd over Pd (p-values ranging from 0.0002 to 0.0009).

Subgroup analysis of the primary outcome

Pre-specified subgroup analyses demonstrated a positive treatment effect with IsaPd vs Pd (HR values ranging from 0.479 to 0.827) in all subgroups considered, consistent with the overall PFS analysis. In addition, the analyses showed no significant interaction at the 10% alpha level for treatment arms vs stratification factors, treatment arms vs demographic characteristics, or treatment arms vs patients' baseline characteristics, indicating an overall consistent treatment effect across those subgroups.

Multivariate analyses of the primary outcome

Multivariate analyses of PFS, adjusted for demographic and baseline characteristics (i.e. 'race' [Asian vs White], 'race' [Other vs White], 'regulatory region' [Western countries vs other countries], 'R-ISS staging at study entry' [II vs I], 'R-ISS staging at study entry' [III vs I], 'refractory to lenalidomide' [Yes vs No]), were included in the final model. The

difference in HR after adjustment (adjusted hazard of 0.484 vs 0.596 for the primary analysis stratified by stratification factors) suggested that there could have been some confounding factors among the analysed covariates that may have influenced the treatment effect in the primary analysis in favour of the Pd arm.

ICARIA-MM – Patients at 4L of treatment

In the 4L population (N=52 and N=58 in the IsaPd and Pd arms, respectively), median PFS was prolonged in the IsaPd arm (13.31 months [95% CI; 7.425, not calculable [NC]) in comparison with the Pd arm (7.82 months [95% CI; 4.468, 11.072]) (Table 12 and Figure 14). The stratified hazard ratio was 0.598 (95% CI; 0.348, 1.030) representing a 40.2% risk reduction of disease progression or death in favour of IsaPd vs Pd. A total of 29 (55.8%) and 25 (43.1%) of these 4th patients in the IsaPd and Pd arms, respectively, had not had a PFS event and were censored.

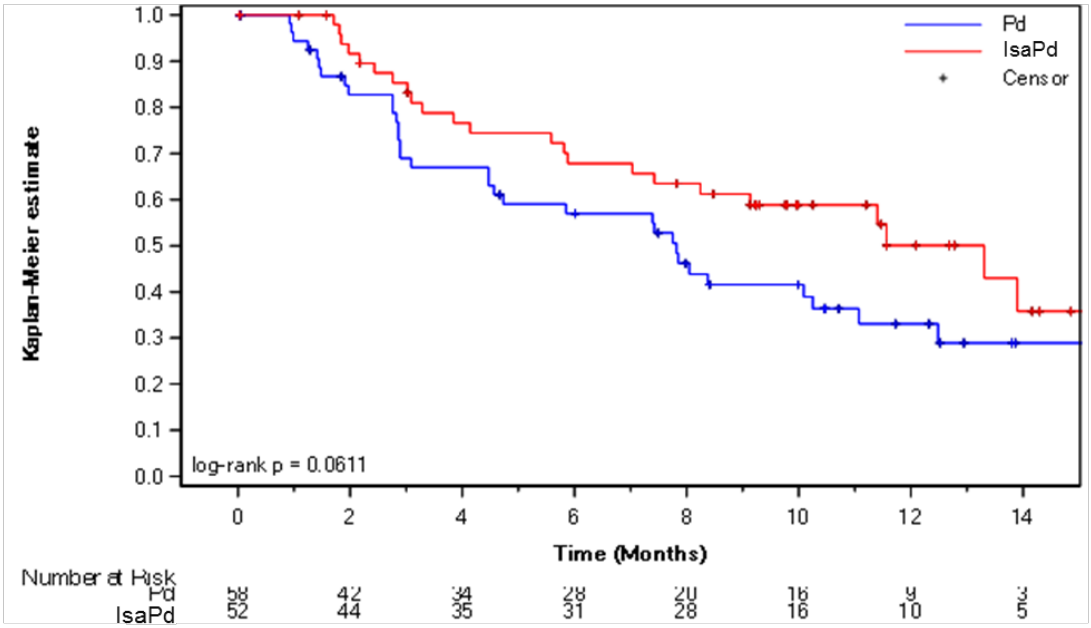
Table 12: ICARIA-MM primary efficacy outcome – PFS† by treatment group, 4L patients by treatment group

	Pd (N=58)	IsaPd (N=52)
Number (%) of events	33 (56.9)	23 (44.2)
Number (%) of patients censored	25 (43.1)	29 (55.8)
Kaplan-Meier estimates of PFS in months		
25% quantile (95% CI)	2.86 (1.478; 4.468)	4.14 (2.431; 8.246)
Median (95% CI)	7.82 (4.468; 11.072)	13.31 (7.425; NC)
75% quantile (95% CI)	NC (10.251; NC)	NC (13.306; NC)
Stratified‡ Log-Rank test p-value§ vs Pd	0.0611	
Stratified‡ HR (95% CI) vs Pd	0.598 (0.348; 1.030)	
PFS probability (95% CI)¶		
2 months	0.827 (0.694; 0.906)	0.917 (0.793; 0.968)
4 months	0.670 (0.523; 0.780)	0.766 (0.617; 0.863)
6 months	0.570 (0.423; 0.692)	0.679 (0.524; 0.792)
8 months	0.462 (0.319; 0.593)	0.635 (0.480; 0.755)
10 months	0.416 (0.276; 0.549)	0.589 (0.433; 0.715)
12 months	0.331 (0.197; 0.471)	0.501 (0.328; 0.651)
14 months	0.289 (0.156; 0.437)	0.358 (0.166; 0.555)
Number of patients at risk¶		
2 months	42	44
4 months	34	35
6 months	28	31
8 months	20	28
10 months	16	16

	Pd (N=58)	IsaPd (N=52)
12 months	9	10
14 Months	3	5

†As per cut-off date: 11th October 2018. Primary analysis based on disease assessment by the IRC.
‡Stratified by age (<75 years vs ≥75 years) according to IRT. §One-sided significance level: 0.025.
¶Estimated using the Kaplan-Meier method.
Abbreviations: CI, confidence interval; NC, not calculable; HR, hazard ratio; IRC, independent response committee; IRT, interactive response technology; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ITT, intention-to-treat; low-dose dexamethasone; MM, multiple myeloma; Pd, pomalidomide; PFS, progression free survival.

Figure 14: ICARIA-MM primary endpoint – PFS† – Kaplan-Meier curves by treatment group, 4L population



Cut-off date: 11th October 2018.
Log-rank p-value stratified by age (<75 years vs ≥75 years) according to IRT. One-sided significance level: 0.025.
Abbreviations: IRT, interactive response technology; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ITT, intention-to-treat; MM, multiple myeloma; Pd, pomalidomide, low-dose dexamethasone; PFS, progression free survival.

B.2.6.1.2 Key secondary efficacy outcomes

Overall response rate (ORR)

ICARIA-MM – ITT population

The ORR based on the IRC assessment was statistically significantly better in the IsaPd arm than in the Pd arm (60.4% vs 35.3%; p<0.0001) (Table 13). In addition, the depth of response (very good partial response [VGPR] or better) observed in the IsaPd group was significantly improved in comparison with that in the Pd group (31.8% vs 8.5%; p<0.0001). A complete response (CR) or better was observed in 4.5% of patients in the IsaPd arm vs 2.0% of patients in the Pd arm, although the proportion of patients with CR in the IsaPd was likely to be underestimated; isatuximab interferes with M-protein measurements in the immunofixation test, thus it is possible that some patients with near-CR (i.e. who met all criteria for a complete response except that immunofixation remained positive) had, in fact, a CR with IsaPd treatment (see Appendix F). The clinical benefit rate (minimal response [MR] or better) was also higher in the IsaPd arm compared with the Pd arm (66.9% vs 46.4%).

Results for the subgroup analyses of ORR, were consistent with those for the primary analysis.

Table 13: ICARIA-MM secondary efficacy outcome – ORR[†] (ITT population)[‡]

	Pd (N=153)	**IsaPd (N=154)**
BOR, n (%)		
sCR	1 (0.7)	0
CR	2 (1.3)	7 (4.5)
VGPR	10 (6.5)	42 (27.3)
Biochemical CR but with missing bone marrow[§]	2 (1.3)	9 (5.8)
Near-CR[¶]	5 (3.3)	24 (15.6)
PR	41 (26.8)	44 (28.6)
MR	17 (11.1)	10 (6.5)
Stable disease	45 (29.4)	33 (21.4)
Non-PD	3 (2.0)	4 (2.6)
PD	14 (9.2)	6 (3.9)
Unconfirmed PD	4 (2.6)	1 (0.6)
Not evaluable/Not assessed	16 (10.5)	7 (4.5)
OR		
Responders (sCR, CR, VGPR or PR), n (%)	54 (35.3)	93 (60.4)
95% CI[††]	0.2775; 0.4342	0.5220; 0.6817
Stratified Cochran-Mantel-Haenszel test p-value[‡‡] vs Pd	<0.0001	

	Pd (N=153)	IsaPd (N=154)
VGPR or better, n (%)	13 (8.5)	49 (31.8)
95% CI††	0.0460; 0.1409	0.2455; 0.3980
Stratified Cochran-Mantel-Haenszel test p-value‡‡ vs Pd	<0.0001	
Clinical benefit		
Responders (MR or better),n (%)	71 (46.4)	103 (66.9)
95% CI††	0.3832; 0.5464	0.5885; 0.7425

†Outcome analysis based on the IRC assessment using the IMWG criteria. ‡As per cut-off date: 11th October 2018. §Two consecutive negative M-protein and negative immunofixation with missing bone marrow. ¶All criteria for a complete response were met except that immunofixation remained positive. ††Estimated using Clopper-Pearson method. ‡‡ Stratified by age (<75 years vs ≥75 years) and number of previous lines (2 or 3 vs >3) according to IRT. One-sided significance level: 0.025.
Biochemical CR and Near-CR were assessed only for patients with confirmed VGPR as BOR. Criteria for confirmation was not applied to Near-CR subcategory.
Abbreviations: BOR, best overall response; CR, complete response; CI, confidence interval; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; IRC, Independent Response Committee, IRT, interactive response technology; ITT, intention-to-treat; MM, multiple myeloma; MR, minimal response; N/n, number of patients; Pd, pomalidomide, low-dose dexamethasone; PD, progressive disease; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

ICARIA-MM – Patients at 4L of treatment

The ORR for patients in 4L, based on the IRC assessment was numerically better in the IsaPd arm than in the Pd arm (53.8% vs 46.6%; p=0.3991) (Table 14). In addition, the depth of response (very good partial response [VGPR] or better) observed in the IsaPd group was improved in comparison with that in the Pd group (26.9% vs 15.5%; p=0.1552). A complete response (CR) or better was observed in 1.9% of patients in the IsaPd arm vs 3.4% of patients in the Pd arm, although the proportion of patients with CR in the IsaPd was likely to be underestimated; isatuximab interferes with M-protein measurements in the immunofixation test, thus it is possible that some patients with near-CR (i.e. who met all criteria for a complete response except that immunofixation remained positive) had, in fact, a CR with IsaPd treatment. The clinical benefit rate (minimal response [MR] or better) was slightly higher in the IsaPd arm compared with the Pd arm (61.5% vs 58.6%).

Table 14: ICARIA-MM secondary efficacy outcome – ORR† by treatment group, 4L population

	Pd (N=58)	IsaPd (N=52)
BOR, n (%)		
sCR	0	0
CR	2 (3.4)	1 (1.9)
VGPR	7 (12.1)	13 (25.0)
Biochemical CR but with missing bone marrow‡	1 (1.7)	2 (3.8)
Near-CR§	4 (6.9)	9 (17.3)
PR	18 (31.0)	14 (26.9)
MR	7 (12.1)	4 (7.7)
Stable disease	20 (34.5)	9 (17.3)
Non-PD	0	2 (3.8)
PD	3 (5.2)	4 (7.7)
Unconfirmed PD	0	1 (1.9)
Not evaluable/Not assessed	1 (1.7)	4 (7.7)
OR		
Responders (sCR, CR, VGPR or PR), n (%)	27 (46.6)	28 (53.8)
95% CI¶	0.3334; 0.6013	0.3947; 0.6777
Stratified Cochran-Mantel-Haenszel test p-value†† vs Pd	0.3991	
VGPR or better, n (%)	9 (15.5)	14 (26.9)
95% CI¶	0.0735; 0.2742	0.1557; 0.4102
Stratified Cochran-Mantel-Haenszel test p-value†† vs Pd	0.1552	
Clinical benefit		
Responders (MR or better), n (%)	34 (58.6)	32 (61.5)
95% CI¶	0.4493; 0.7140	0.4702; 0.7470

†As per cut-off date: 11th October 2018. ‡Two consecutive negative M-protein and negative immunofixation with missing bone marrow. §All criteria for a complete response were met except that immunofixation remained positive. ¶Estimated using Clopper-Pearson method. ††Stratified by age (<75 years vs ≥75 years) and number of previous lines (2 or 3 vs >3) according to IRT. One-sided significance level: 0.025.
Biochemical CR and Near-CR were assessed only for patients with confirmed VGPR as BOR. Criteria for confirmation was not applied to Near-CR subcategory.
Abbreviations: BOR, best overall response; CR, complete response; CI, confidence interval; IRC, Independent Response Committee, IRT, interactive response technology; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ITT, intention-to-treat; MM, multiple myeloma; MR, minimal response; N/n, number of patients; Pd, pomalidomide, low-dose dexamethasone; PD, progressive disease; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

Overall survival (OS)

ICARIA-MM – ITT population

At the cut-off date, an interim analysis of OS for IsaPd and Pd was conducted by means of a log-rank test, with a one-side significance level of 0.0008 (determined by using O'Brien and Fleming α-spending function).

A total of 99 death events (45% of the targeted 220 events to achieve 80% statistical power) were reported (43 in IsaPd arm and 56 in Pd arm) (Table 15). Among patients who were censored, most were alive at the cut-off date or alive at the last contact before the cut-off date, and only 3.6% in the IsaPd arm and 7.2% in the Pd arm were lost to follow-up (time from last contact to analysis cut-off date >8 weeks). At a median follow-up of 11.56 and 11.73 months in the IsaPd and Pd arms, respectively, a trend toward longer OS, with an early separation of the survival curves (Figure 15), was observed in patients who received IsaPd compared with Pd (HR=0.687; [95% CI; 0.461, 1.023]), but median OS had not been reached in either treatment arm. At the time of the analysis, the probability of surviving (95% CI) 12 months was 0.720 (95% C; 0.636, 0.787) in the IsaPd arm and 0.633 (95% CI; 0.545, 0.709) in the Pd arm. Further follow-up is ongoing.

At the analysis cut-off date, 54.2% of patients in the Pd arm receiving subsequent treatment had received daratumumab (other anti-CD38) therapy. In addition, 6 patients in the IsaPd arm received daratumumab after definitive treatment discontinuation (Table 16).

Thus, the observed trend towards longer OS in the Pd arm should be interpreted with caution in the Pd arm, taking into consideration high levels of censoring and in the context subsequent therapy (in particular, daratumumab).

A sensitivity analysis was conducted to evaluate the treatment effect on OS, in the absence of switch to subsequent anti-cancer therapy with daratumumab. The resulting stratified HR was 0.708 (95% CI; 0.451, 1.111) (Table 17) which is consistent with the stratified HR of 0.687 (95% CI; 0.461, 1.023) in the OS primary analysis. These results should be interpreted with caution as all factors contributing to the shift to daratumumab may have not been captured in the model.

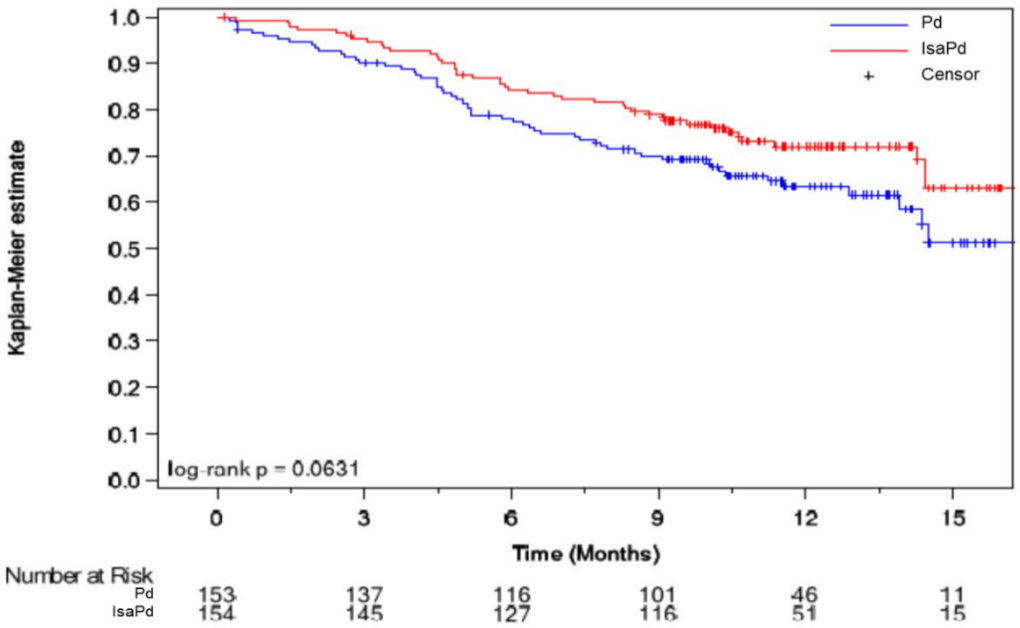
Results for the subgroup analyses of OS, showed an improvement in OS favouring the IsaPd arm over the Pd arm, in patients with renal function impairment, consistent with the improvement observed for PFS and ORR. Nevertheless, the results should be interpreted with caution due to immaturity of data.

Table 15: ICARIA-MM secondary efficacy outcome – OS[†] (ITT population)

	Pd (N=153)	IsaPd (N=154)
Number (%) of deaths	56 (36.6)	43 (27.9)
Number (%) of patients censored	97 (63.4)	111 (72.1)
Reason of censoring		
Alive at the cut-off date	90 (92.8)	106 (95.5)
Alive at the last contact before cut-off date	0	1 (0.9)
Lost to follow-up	7 (7.2)	4 (3.6)
Kaplan-Meier estimates of OS, months		
25% quantile (95% CI)	6.60 (5.027; 10.086)	10.64 (7.688; 14.456)
Median (95% CI)	NC (13.897; NC)	NC
75% quantile (95% CI)	NC	NC
Stratified[‡] Log-Rank test p-value[§] vs Pd	0.0631	
Stratified[‡] HR[¶] (95% CI) vs Pd	0.687 (0.461; 1.023)	
Survival probability (95% CI)[††]		
3 months	0.901 (0.842; 0.939)	0.954 (0.906; 0.978)
6 months	0.781 (0.706; 0.839)	0.842 (0.774; 0.891)
9 months	0.700 (0.619; 0.767)	0.789 (0.715; 0.846)
12 months	0.633 (0.545; 0.709)	0.720 (0.636; 0.787)
15 months	0.512 (0.376; 0.632)	0.631 (0.504; 0.733)
Number of patients at risk[††]		
3 months	137	145
6 months	116	127
9 months	101	116
12 months	46	51
15 months	11	15

†As per cut-off date: 11th October 2018. ‡Stratified by age (<75 years vs ≥75 years) and number of previous lines of therapy (2 or 3 vs >3) according to IRT. §One-sided significance level: 0.025. ¶HR<1 favours IsaPd arm. ††Estimated using the Kaplan-Meier method.
Abbreviations: CI, confidence interval; HR, hazard ratio; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ITT, intention-to-treat; MM, multiple myeloma; NC, not calculable; OS, overall survival; Pd, pomalidomide, low-dose dexamethasone.

Figure 15: ICARIA-MM key secondary endpoint – OS† – Kaplan-Meier curves by treatment group (ITT population)



†Cut-off date: 11th October 2018.
Log-rank p-value stratified by age (<75 years vs ≥75 years) and number of previous lines of therapy (2 or 3 vs >3) according to IRT. One-sided significance level: 0.0008 (obtained using the O'Brien-Fleming α-spending function for the interim analysis).
Abbreviations: IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ITT, intention-to-treat; MM, multiple myeloma; Pd, pomalidomide, low-dose dexamethasone.

Table 16: ICARIA-MM - further anti-myeloma treatments (ITT population)

	Pd (N=153)	IsaPd (N=154)
Number (%) of patients with any further anti-myeloma treatment	83 (54.2)	60 (39.0)
Number of further regimens		
Mean (SD)	1.4 (0.9)	1.4 (0.8)
1, n (%)	54 (69.2)	39 (68.4)
2, n (%)	16 (20.5)	13 (22.8)
≥3, n (%)	8 (10.3)	5 (8.8)
Main further anti-myeloma treatments by class and agent, n (%)		
Alkylating agents	33 (39.8)	40 (66.7)
PI	39 (47.0)	34 (56.7)
IMiDs	19 (22.9)	14 (23.3)
HDAC inhibitors	2 (2.4)	3 (5.0)
Anthracyclins	7 (8.4)	6 (10.0)
Corticosteroids	59 (71.1)	51 (85.0)
Monoclonal antibodies	45 (54.2)	6 (10.0)

	Pd (N=153)	IsaPd (N=154)
Daratumumab	45 (54.2)	6 (10.0)

Abbreviations: HDAC, histone deacetylase; IMiDs, immunomodulatory drugs, IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ITT, intention-to-treat; MM, multiple myeloma; Pd, pomalidomide, low-dose dexamethasone; PI, proteasome inhibitors; SD, standard deviation.

Table 17: ICARIA-MM secondary efficacy outcome – Sensitivity† analysis adjusting OS‡ for switch to daratumumab (ITT population)

	Pd (N=153)	IsaPd (N=154)
Number (%) of deaths	40 (26.1)	38 (24.7)
Number (%) of patients censored	113 (73.9)	116 (75.3)
HR§ (95% CI) vs Pd	0.668 (0.426; 1.049)	
Stratified¶ HR§ (95% CI) vs Pd	0.708 (0.451; 1.111)	

†Estimated using IPCW method. ‡As per cut-off date: 11th October 2018. §HR<1 favours IsaPd arm. ¶Stratified by age (<75 years vs ≥75 years) and number of previous lines of therapy (2 or 3 vs >3) according to IRT.
Abbreviations: CI, confidence interval; HR, hazard ratio; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; IPCW, inverse probability of censoring weighting; ITT, intention-to-treat; MM, multiple myeloma; OS, overall survival; Pd, pomalidomide, low-dose dexamethasone.

ICARIA-MM – Patients at 4L of treatment

At the cut-off date, 69% of the 4L patients were still alive (41 in IsaPd arm and 35 in Pd arm) at a median follow-up of 11.6 months, and were, consequently, censored in the data analysis (Table 18). Although OS was immature, a trend towards longer OS in IsaPd (vs Pd) was observed, with a median OS of 14.36 months in the Pd arm while in the IsaPd it had not been reached (Figure 16). The stratified HR was 0.494 (95% CI; 0.240, 1.015), representing a 51% risk reduction of death in favour of IsaPd vs Pd (Table 18). At the time of the analysis, the probability of surviving (95% CI) 12 months was 0.780 (95% CI; 0.638, 0.872) in the IsaPd arm and 0.619 (95% CI; 0.474; 0.735) in the Pd arm. Further follow-up is ongoing.

At the cut-off date, 16 (27.6%) of the 4th patients in the Pd arm had received daratumumab (other anti-CD38) as subsequent therapy. In addition, 2 (3.8%) of the 4L patients in the IsaPd arm received daratumumab as subsequent treatment (Table 19). The use of daratumumab in patients who progress at 4L is unlikely to reflect UK clinical practice and, therefore, may impact the generalisability of the study results to the UK.

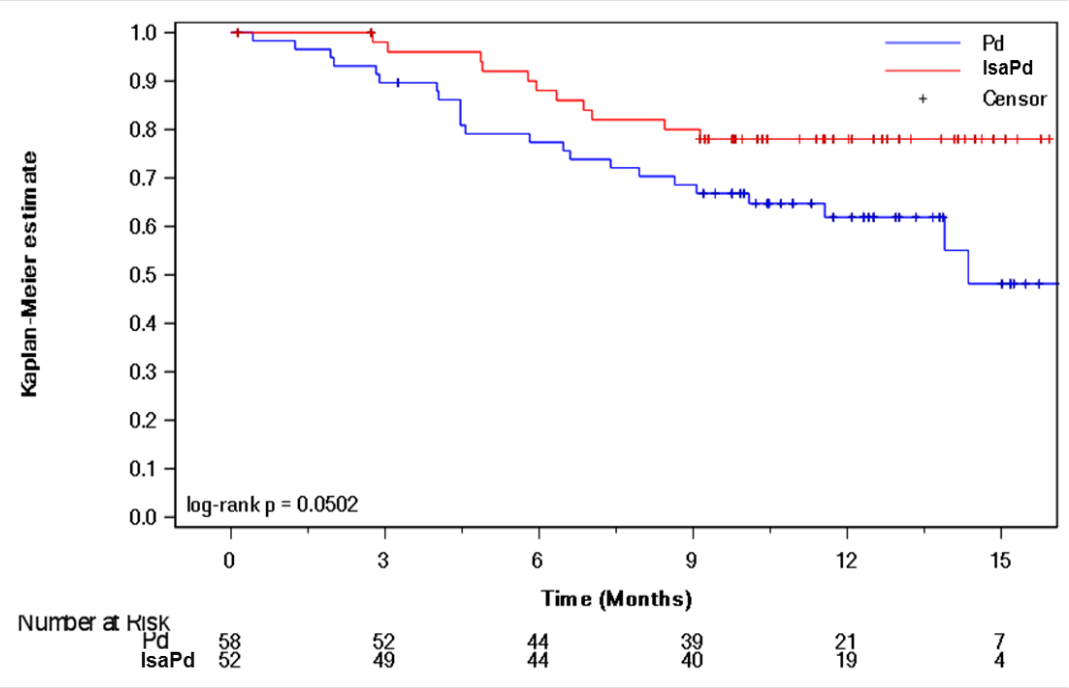
Thus, the observed trend towards longer OS should be interpreted with caution, taking into consideration high levels of censoring and in the context subsequent therapy (in particular with daratumumab).

Table 18: ICARIA-MM secondary efficacy outcome – OS† by treatment group, 4L population

	Pd (N=58)	IsaPd (N=52)
Number (%) of deaths	23 (39.7)	11 (21.2)
Number (%) of patients censored	35 (60.3)	41 (78.8)
Kaplan-Meier estimates of OS, months		
25% quantile (95% CI)	6.60 (4.041; 11.565)	NC (6.341; NC)
Median (95% CI)	14.36 (11.565; NC)	NC (NC; NC)
75% quantile (95% CI)	NC (NC; NC)	NC (NC; NC)
Stratified‡ Log-Rank test p-value§ vs Pd	0.0502	
Stratified‡ HR (95% CI) vs Pd	0.494 (0.240; 1.015)	
Survival probability (95% CI)¶		
3 months	0.897 (0.784; 0.952)	0.980 (0.866; 0.997)
6 months	0.773 (0.642; 0.862)	0.880 (0.752; 0.944)
9 months	0.686 (0.548; 0.789)	0.800 (0.660; 0.887)
12 months	0.619 (0.474; 0.735)	0.780 (0.638; 0.872)
15 months	0.481 (0.279; 0.658)	0.780 (0.638; 0.872)
Number of patients at risk¶		
3 months	52	49
6 months	44	44
9 months	39	40
12 months	21	19
15 months	7	4

†As per cut-off date: 11th October 2018. ‡Stratified by age (<75 years vs ≥75 years) according to IRT. §One-sided significance level: 0.025. ¶Estimated using the Kaplan-Meier method.
Abbreviations: CI, confidence interval; HR, hazard ratio; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ITT, intention-to-treat; MM, multiple myeloma; NC, not calculable; OS, overall survival; Pd, pomalidomide, low-dose dexamethasone.

Figure 16: ICARIA-MM key secondary endpoint – OS† – Kaplan-Meier curves by treatment group, 4L population



†Cut-off date: 11th October 2018.
Log-rank p-value stratified by age (<75 years vs ≥75 years) according to IRT. One-sided significance level: 0.025.
Abbreviations: IRT, interactive response technology; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ITT, intention-to-treat; MM, multiple myeloma; OS, overall survival; Pd, pomalidomide, low-dose dexamethasone

Table 19: ICARIA-MM secondary efficacy outcome – OS[†]– subgroup analyses by further therapy with daratumumab, 4L population

	Pd			IsaPd			HR (95% CI) vs Pd	p-value for interaction[‡]
	N	Events, n (%)	Median (Months) (95% CI)	N	Events, n (%)	Median (Months) (95% CI)		
All patient	58	23 (39.7)	14.357 (11.565; NC)	52	11 (21.2)	NC (NC; NC)	0.506 (0.245; 1.045)	
Further therapy with daratumumab								0.3496
Yes	42	17 (40.5)	NC (8.641; NC)	50	10 (20.0)	NC (NC; NC)	0.441 (0.202; 0.964)	
No	16	6 (37.5)	14.357 (7.392; NC)	2	1 (50.0)	NC (4.862; NC)	1.040 (0.117; 9.212)	

†Cut-off date: 11th October 2018. ‡Interaction test from the Cox proportional hazard model including the factor, treatment effect and the treatment by factor interaction.
Abbreviations: CI, confidence interval; HR, hazard ratio; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; IPCW, inverse probability of censoring weighting; ITT, intention-to-treat; MM, multiple myeloma; OS, overall survival; Pd, pomalidomide, low-dose dexamethasone.

B.2.6.1.3 Other secondary efficacy outcomes

A summary of the results for other secondary efficacy outcomes assessed in the ICARIA-MM trial, is presented in Table 20.

Table 20: Summary of the results for other secondary efficacy outcomes[†] in the ICARIA-MM trial (ITT population)

Secondary efficacy outcome	ICARIA-MM – ITT population		ICARIA-MM –4L patients	
	Pd (N=153)	IsaPd (N=154)	Pd (N=58)	IsaPd (N=52)
TTP, median (months) (95% CI)	7.75 (5.027; 9.758)	12.71 (11.203; 15.211)	8.05 (5.848; NC)	13.31 (8.246; NC)
High-risk cytogenetic population				
PFS				
High cytogenetic risk				
Median (months) (95% CI)	3.745 (2.793; 7.885)	7.491 (2.628; NC)	2.825 (1.446; 11.072)	7.031 (1.807; NC)
HR (95%)	0.655 (0.334; 1.283)		0.683 (0.222; 2.102)	
Chromosomal abnormality del(17p)				
Median (months) (95% CI)	7.392 (2.793; 11.072)	9.133 (1.807; NC)	7.392 (1.248; NC)	5.552 (1.807; 9.133)
HR (95%)	0.764 (0.304; 1.918)		1.141 (0.254; 5.131)	
ORR				
High cytogenetic risk				
N (%) responders[‡] (95% CI)	6 (16.7) (0.0637; 0.3281)	12 (50.0) (0.2912; 0.7088)	7 (53.8) (0.2513; 0.8078)	4 (50.0) (0.1570; 0.8430)
Chromosomal abnormality del(17p)				
N (%) responders[‡] (95% CI)	5 (21.7) (0.0746; 0.4370)	7 (50.0) (0.2304; 0.7696)	5 (50.0) (0.1871; 0.8129)	1 (20.0) (0.0051; 0.7164)
DOR[δ]				
Median (months) (95% CI)	11.07 (8.542; NC)	13.27 (10.612; NC)	NC (6.867; NC)	NC (12.025; NC)
Stratified[¶] HR (95%) vs Pd	0.828 (0.464; 1.474)		0.626 (0.222; 1.766)	

Secondary efficacy outcome	ICARIA-MM – ITT population		ICARIA-MM –4L patients	
	Pd (N=153)	IsaPd (N=154)	Pd (N=58)	IsaPd (N=52)
TT1R, median (months) (95% CI)	3.02 (2.825; 5.060)	1.94 (1.314; 2.004)	3.02 (1.938; NC)	1.91 (1.150; 3.055)
TTBR, median (months) (95% CI)	5.06 (3.778; 7.885)	4.30 (2.891; 5.125)	6.51 (3.023; NC)	5.16 (3.055; 5.749)
MRD††, n_{Total}				
MRD negative at sensitivity level:				
10^{-4}	0	10	0	5
10^{-5}	0	8	0	4
10^{-6}	0	2	0	1
MRD positive at sensitivity level:				
10^{-4}	2	4	—	—
10^{-5}	2	6	—	—
10^{-6}	2	9	—	—

†As per cut-off date: 11th October 2018. ‡ Response: sCR, CR, VGPR or PR. δDuration of response is determined only for patients (ITT population: N=54 in the Pd arm and N=93 in the IsaPd arm; Patients at 4L: N=22 in the Pd arm and N=31 in the IsaPd arm) who have achieved a response of PR or better (subsequently confirmed) based on disease assessment by IRC. ¶Estimated using the Kaplan-Meier method. Bone marrow samples for MRD assessment were collected by Investigator in case of Investigator-assessed CR or if clinically indicated. ††MRD data were available for 14 patients in the IsaPd arm and 2 patients in the Pd arm, in the whole ICARIA-MM population, and 5 patients in the IsaPd arm and 1 patient in the Pd arm .

Abbreviations: CI, confidence interval; CR, complete response; DOR, duration of response; HR, hazard ratio; IRC, Independent Response Committee; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ITT, intention-to-treat; MM, multiple myeloma; MRD, minimal residual disease; NA, not applicable; NC, not calculable; ORR, overall response rate; Pd, pomalidomide, low-dose dexamethasone; POR, patient-reported outcomes; PR, partial response; sCR, stringent complete response; TT1R, Time to first response; TTP, time to progression; VGPR, very good partial response

B.2.6.1.4 Additional evidence of clinical benefit

Renal impairment

Renal function impairment was defined as creatinine clearance [MDRD] <60 mL/min/1.73m^2. Disease-specific characteristics at baseline showed a trend towards more patients with renal impairment in the IsaPd arm than in the Pd arm (38.7% vs 33.8%) (Section B.2.3.1.2). During treatment, there was a trend towards less deterioration in renal function in the IsaPd arm (Table 21). In the overall population, the number of patients who progressed to severe or end stage renal impairment (<30 mL/min/1.73m^2) was lower in the IsaPd arm than in the Pd arm (12.9% vs 18.6%), which was due to fewer patients having end stage disease in the IsaPd arm than the Pd arm (2.9% vs 7.9%). Among patients who entered with moderate renal impairment (creatinine clearance [MDRD] ≥30–<60 mL/min/1.73m^2), fewer patients in the IsaPd arm (12/53, 22.6%) developed worsening of renal function to severe renal impairment or end-stage renal disease compared with the Pd arm (16/46, 34.8%).

Table 21: ICARIA-MM additional clinical evidence – renal function (safety population)

Laboratory parameter n/N1 (%)†	Pd (N=149)	IsaPd (N=152)
Creatinine clearance (MDRD)		
≥60–<90 mL/min/1.73m^2 (mild impairment)	52/140 (37.1)	55/140 (39.3)
≥30–<60 mL/min/1.73m^2 (moderate impairment)	53/140 (37.9)	55/140 (39.3)
≥15–<30 mL/min/1.73m^2 (severe impairment)	15/140 (10.7)	14/140 (10.0)
<15 mL/min/1.73m^2 (end stage renal disease)	11/140 (7.9)	4/140 (2.9)
Creatinine increased		
All Grades	136/147 (92.5)	131/152 (86.2)
Grade 1	106/147 (72.1)	110/152 (72.4)
Grade 2	17/147 (11.6)	17/152 (11.2)
Grade 3	13/147 (8.8)	4/152 (2.6)
Grade 4	0/147	0/152
Hyperuricemia		
All Grades	57/147 (38.8)	57/152 (37.5)
Grade 1	0/147	0/152
Grade 2	0/147	0/152
Grade 3	48/147 (32.7)	47/152 (30.9)
Grade 4	9/147 (6.1)	10/152 (6.6)
Blood Urea Nitrogen, ≥ 17 mmol/L	5/61 (8.2)	6/67 (9.0)

†Percentage calculated using the number of patients with at least one event (n) over the number of patients assessed for each parameter (N1) during the on-treatment period.
Abbreviations: IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; MM, multiple myeloma; MDRD, Modification of Diet in Renal Disease; N/n, number of patients; Pd, pomalidomide, low-dose dexamethasone.

Renal response

A complete renal response (CRenal) was defined as an improvement in creatinine clearance from <50 mL/min/1.73 m^2 at baseline to ≥60 mL/min/1.73m^2 at ≥1 post-baseline assessment and a durable CRenal was a response was one that lasted ≥60 days (67). A minor renal response (MRenal) was defined as an improvement to ≥1 creatinine clearance assessment ≥30 mL/min/1.73m^2 during treatment. During treatment, more patients in the IsaPd arm than the Pd arm had a CRenal and durable CRenal, and fewer patients in the IsaPd arm progressed to end stage renal disease. A CRenal was observed in 23 (71.9%) patients in the IsaPd arm and in 8 (38.1%) of patients in the Pd arm (Table 22). Sustained CRenal (duration of response ≥60 days) occurred in 10 (31.3%) patients in the IsaPd arm and in 4 (19.0%) patients in Pd arm. One patient in the IsaPd arm had MRenal.

Table 22: ICARIA-MM additional clinical evidence – renal response (ITT population)

	Pd (N=153)	IsaPd (N=154)
Patients with creatinine clearance (MDRD) <50 mL/min/1.73m^2 at baseline, N1	21	32
Crenal: <50 mL/min/1.73m^2 at baseline and at least one assessment ≥60 mL/min/1.73m^2 during treatment, n/N1 (%)[†]	8/21 (38.1)	23/32 (71.9)
Patients with creatinine clearance (MDRD) <15 mL/min/1.73m^2 at baseline	0	0
Patients with creatinine clearance (MDRD) ≥15–<30 mL/min/1.73m^2 at baseline, N1	0	1
MRenal: ≥15–<30 mL/min/1.73m^2 at baseline and at least one assessment ≥30–<60 mL/min/1.73m^2 during treatment, n/N1 (%)[†]	0	1/1 (100)

[†]Percentage calculated using the number of patients with both baseline and at least one assessment post-baseline.
Notes: Patients may be counted in more than one category.
Abbreviations: CRenal, complete renal response; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ITT, Intention-to-treat; MM, multiple myeloma; MDRD, Modification of Diet in Renal Disease; MRenal, minor renal response; N/n, number of patients; Pd, pomalidomide, low-dose dexamethasone.

PFS, ORR, and OS in patients with renal function impairment at baseline

A consistent treatment effect was observed for efficacy parameters in patients who entered the study with renal function impairment. In this population, the IsaPd arm showed greater improvement compared with the Pd arm for median PFS (3.745 vs 9.495 months, HR=0.502 [95% CI; 0.297; 0.847]); ORR (56.4% vs 24.5%); and VGPR or better (32.7% vs 4.1%). At the time of the analysis, a clear trend in OS was observed: median OS was 11.6 months in Pd arm and not reached yet in IsaPd arm; the HR for OS was 0.534 (95% CI; 0.298, 0.959), with upper bound of the 95% CI not crossing 1.

Time to next treatment

Overall, there was a greater delay in time to next treatment in the IsaPd arm compared with the Pd arm by the time of the primary analysis (**Table 23**). Fifty-four percent of patients in the Pd arm and 39% of patients in the IsaPd arm received further anti-myeloma therapy. The median time from initiation of treatment to next treatment was not reached in the IsaPd arm and was 9.10 months (95%CI; 6.374,12.255) in the Pd arm, with a HR of 0.538 (95% CI: 0.382 to 0.758), indicating that the addition of isatuximab to Pd treatment resulted in a meaningful delay of the next myeloma therapy. Among patients who received further anti-myeloma treatment (60 and 83 patients in the IsaPd and Pd arms, respectively), subsequent therapy with daratumumab was given less frequently in the IsaPd arm than the Pd arm (10.0% and 54.2%, respectively), IMiD at a

similar frequency (22.3% and 22.9%, respectively), and alkylating agents more frequently in the IsaPd arm (66.7% and 39.8%, respectively).

Table 23: ICARIA-MM additional clinical evidence – TNT† (ITT population)

	Pd (N=153)	IsaPd (N=154)
Number (%) of events	81 (52.9)	56 (36.4)
Number (%) of patients censored	72 (47.1)	98 (63.6)
Kaplan-Meier estimates of TNT in months		
25% quantile (95% CI)	4.21 (2.563; 4.698)	7.43 (5.684; 8.772)
Median (95% CI)	9.10 (6.374; 12.255)	NC (12.123; NC)
75% quantile (95% CI)	NC (14.127; NC)	NC
Stratified‡ HR¶ (95% CI) vs Pd	0.538 (0.382; 0.758)	
TNT probability (95% CI)‡		
2 months	0.140 (0.090; 0.201)	0.059 (0.029; 0.105)
4 months	0.237 (0.172; 0.309)	0.140 (0.090; 0.200)
6 months	0.379 (0.299; 0.458)	0.190 (0.131; 0.257)
8 months	0.472 (0.386; 0.553)	0.270 (0.200; 0.344)
10 months	0.540 (0.451; 0.621)	0.374 (0.293; 0.455)
12 months	0.579 (0.484; 0.662)	0.390 (0.305; 0.475)
14 months	0.635 (0.529; 0.724)	0.453 (0.348; 0.553)
16 months	0.676 (0.546; 0.776)	0.453 (0.348; 0.553)

†As per cut-off date: 11th October 2018. ‡ Estimated using the Kaplan-Meier method.
Abbreviations: CI, confidence interval; NC, not calculable; HR, hazard ratio; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ITT, intention-to-treat; MM, multiple myeloma; N, number of patients; Pd, pomalidomide, low-dose dexamethasone; PFS, progression free survival.

ECOG Performance Status score

Regardless of ECOG PS being considered a safety parameter in the study protocol, results for this parameter are presented under the efficacy section, as they are affected by both patient's treatment response and safety profile.

Improvements in ECOG PS were generally similar in the IsaPd and Pd arms, but deterioration occurred less frequently in the IsaPd arm. In the IsaPd arm, the best ECOG PS was improved 1 point from baseline in 18.4% of patients and by 2 points in 2.6% of patients; in the Pd arm, best ECOG PS was improved 1 point from baseline in 16.1% of patients and no patient improved 2 points. Baseline score was the best score for 116 76.3% of patients in the IsaPd arm and 76.5% patients in the Pd arm. Scores worsened less frequently on treatment in the IsaPd arm (37.5%) than in the Pd arm and (42.3%), with fewer patients in the IsaPd arm than in the Pd arm having worsening of ECOG PS to 3 or 4 (4.6% vs 9.4%). Baseline score was the worst score for 61.2% patients in the IsaPd arm and 53.7% of patients in the Pd arm.

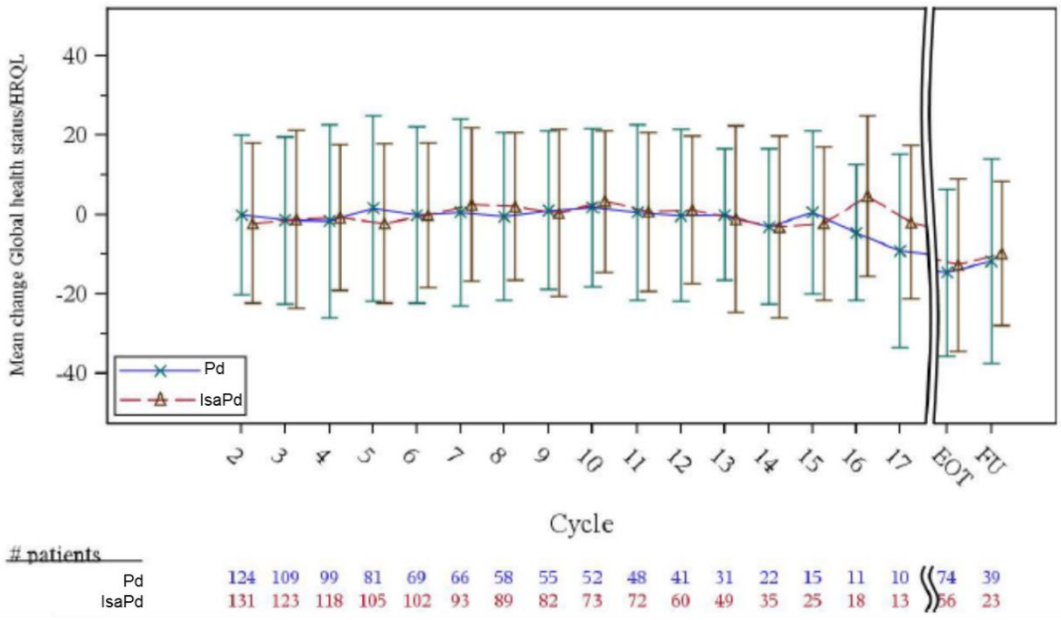
B.2.6.1.5 Health-related quality-of-life (HRQoL)

ICARIA-MM – ITT population

EORTC QLQ-C30

Baseline scores were comparable between the two treatment arms (IsaPd vs Pd: EORTC QLQ-C30 global health status (GHS)/quality of life (QoL) 60.4 vs 59.5; physical functioning (PF) 71.9 vs 72.0; pain 34.5 vs 33.2; fatigue 37.9 vs 35.0). No significant changes from baseline in EORTC QLQ-C30 GHS/QoL was identified for IsaPd vs significant worsening for Pd: change at each cycle was a mean (SD) increase of 0.18 (0.03) points for IsaPd vs a decrement of 0.50 (0.05) for Pd ($p<0.001$) in relation to baseline (Figure 17). For pain and fatigue, no change was observed for IsaPd, while symptom burden increased for Pd: pain per cycle: –0.12 (0.10) points vs +0.44 (0.06) points ($p=0.04$); fatigue per cycle: +0.04 (0.01) points vs +0.49 (0.07) ($p=0.05$). PF scores significantly worsened for Pd but not for IsaPd, and the decline was significantly greater for the Pd arm (per cycle: –0.27 [0.05] vs −0.75 [0.05]; $p=0.01$). The minimal important difference of 10-point change was not reached on any outcome, for either treatment arm. Changes in both pain and PF significantly predicted changes in GHS/QoL in both treatment arms (pain: both $\beta= –0.9$, $p<0.01$; PF: $\beta= 1.2$ IsaPd and $\beta=0.8$ Pd, both $p<0.001$). Changes in fatigue significantly predicted changes in GHS/QoL for the Pd arm ($\beta= –1.0$; $p<0.01$) but not the IsaPd arm ($p=0.29$).

Figure 17: ICARIA-MM key secondary endpoint – Mean CFB for GHS score† over time (safety population‡)



†A higher score represents a better level of quality of life. ‡Patients from the safety population who have completed the baseline and at least one post-baseline assessment.
EOT: 30 days after last study treatment administration; FU: 60 days after last study treatment administration
Note: Cycles with less than 20 patients overall are not presented. Error bars for SD are presented.
Abbreviations: CFB, change from baseline; EOT, end of treatment; FU, follow-up; GHS, global health status; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; MM, multiple myeloma; Pd, pomalidomide, low-dose dexamethasone; SD, standard deviation.

QLQ-MY20

Overall, the scores for body image, future perspective, disease symptoms, and side effects were maintained throughout the treatment period for both treatment arms, based on the absence of clinically important mean change from baseline.

EQ-5D-5L

Overall, health state utility and health status were maintained during the treatment period, based on EQ-5D-5L HSUV and EQ-5D-5L VAS scores. There were some isolated changes of ±10 points or greater in the mean scores towards the end of the treatment period in the Pd arm. However, these results should be interpreted with caution, given the small sample sizes and absence of statistical testing.

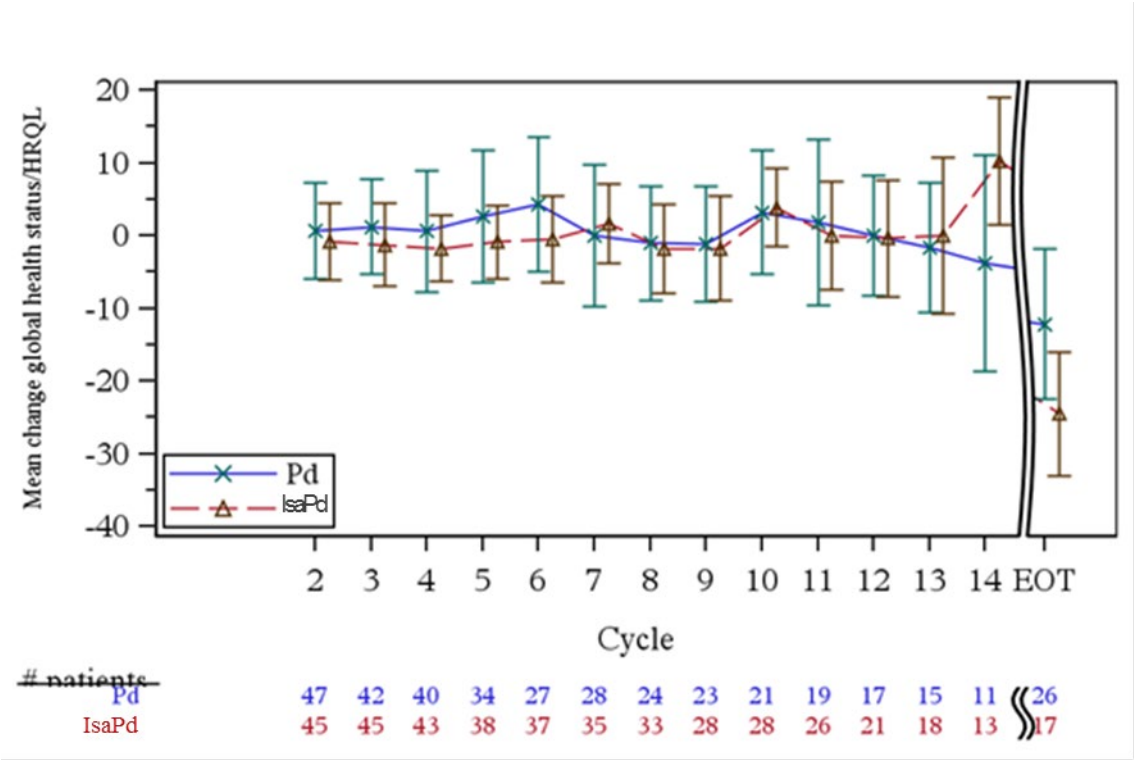
ICARIA-MM – Patients at 4L of treatment

EORTC QLQ-C30

Limited data were available in the 4L patient population to provide similar analysis to that reported above for the ITT population. An exploratory analysis that modelled the pain domain from baseline through to cycle 10 (the model fit becomes unacceptable due to low sample size with any further cycles) found that average change per cycle within each treatment group was not significant, but differences were noted between the groups. These results suggest that IsaPd is associated with no change in pain while Pd is associated with an increase in pain. As the difference between the two treatment groups was larger for the 4L patient model than the ITT population, it may be the case that the sample size has unduly influenced the difference and the results should be treated with caution.

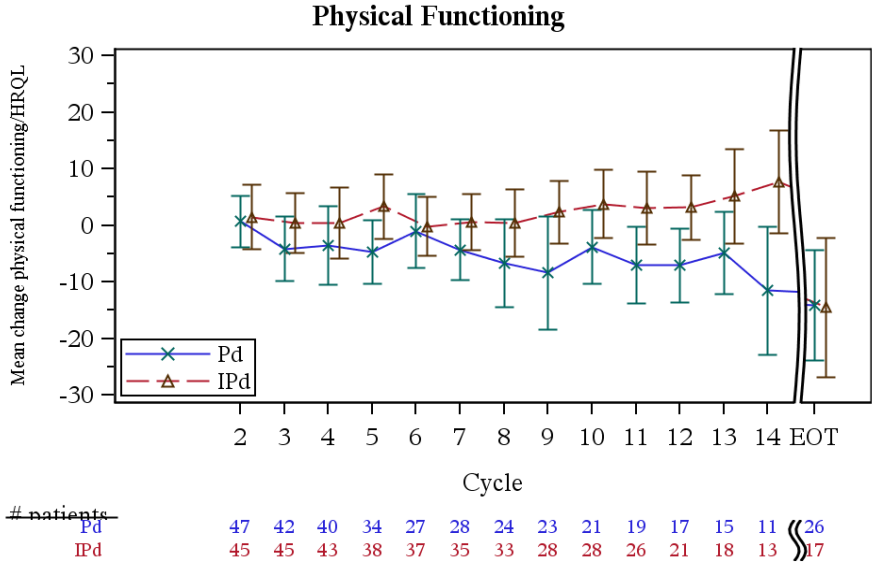
Below we report mean change from baseline to end of the trial for EORTC QLQ-C30 global health status (GHS)/quality of life (QoL) (Figure 18), physical functioning, pain and fatigue (Figure 19). Due to the small sample size, formal statistical comparisons were not made. In general, the results in this subgroup are aligned with those for the ITT population.

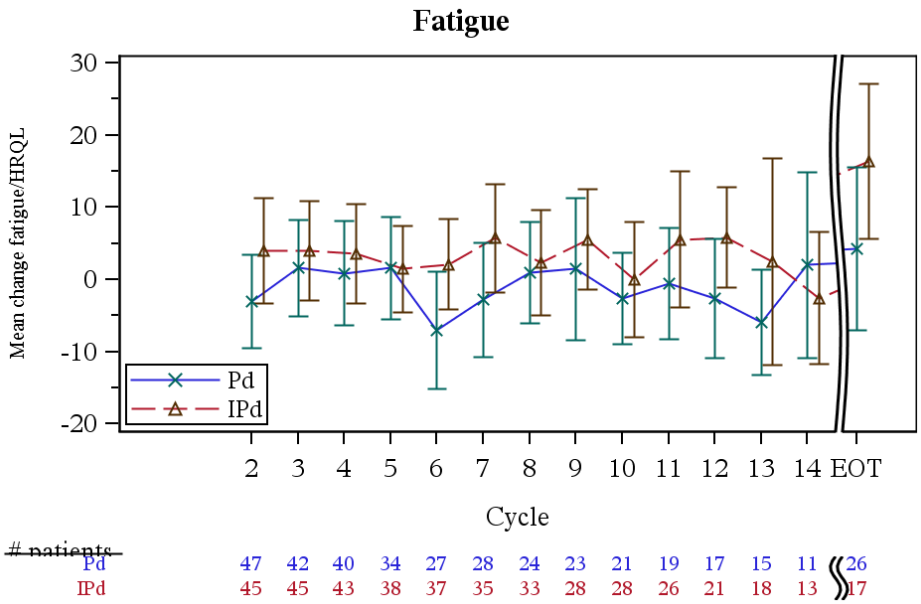
Figure 18: ICARIA-MM key secondary endpoint – EORTC-QLQ-C30-GHS/QoL† – Mean change from baseline for global health status score over time, 4L population

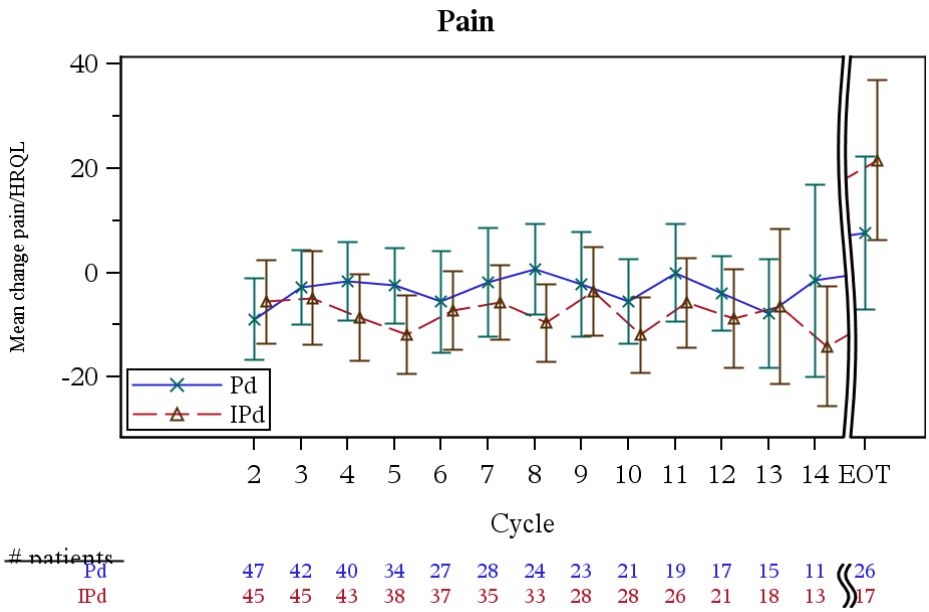


†A higher score represents a better level of quality of life.
End of treatment: 30 days after last study treatment administration. Note: Cycles with less than 20 patients overall are not presented.
Abbreviations: EOT, end of treatment; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire with 30 items; FU, follow-up; GHS, global health status; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; MM, multiple myeloma; Pd, pomalidomide, low-dose dexamethasone; QoL, quality of life.

Figure 19: ICARIA-MM key secondary endpoint – EORTC QLQ-C30† – Mean change from baseline for physical functioning, fatigue and pain scores over time, 4L population







†A higher score represents a better level of quality of life for the following outcomes: 'Physical functioning', 'Role functioning', 'Cognitive functioning', 'Emotional functioning', and 'Social functioning'. A lower score represents a better level of quality of life for the following outcomes: 'Fatigue', 'Nausea and vomiting', 'Pain', 'Dyspnoea', 'Insomnia', 'Appetite loss', 'Constipation', 'Diarrhoea', and 'Financial difficulties'.
End of treatment: 30 days after last study treatment administration. Note: Cycles with less than 20 patients overall are not presented.
Abbreviations: EOT, end of treatment; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire with 30 items; FU, follow-up; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; MM, multiple myeloma; Pd, pomalidomide, low-dose dexamethasone.

EQ-5D-5L

Overall, HRQoL for 4L patients, as measured by EQ-5D-5L health state utility index value (HSUV) (Table 24) and EQ-5D-5L visual analogue scale (VAS) (Table 25), was sustained over time and similar in both treatment groups. At the end of the trial, worsening in health state utility and health status for 4L patients were observed in both treatment groups, but more noticeable in the IsaPd arm. However, these results should be interpreted with caution, given the small sample sizes and absence of statistical testing.

Table 24: ICARIA-MM key secondary endpoint – EQ-5D-5L HSUV, 4L (safety population†)

	Pd (N=53)		**IsaPd (N=49)**	
	Mean (SD)†	CFB	Mean (SD)†	CFB
Baseline	0.66 (0.25)	—	0.74 (0.20)	—
Treatment cycle 2‡	0.71 (0.25)	0.04 (0.24)	0.74 (0.25)	0.00 (0.20)
Treatment cycle 3‡	0.73 (0.21)	0.02 (0.19)	0.73 (0.25)	–0.00 (0.20)
Treatment cycle 4‡	0.74 (0.25)	0.05 (0.27)	0.78 (0.22)	0.04 (0.19)
Treatment cycle 5‡	0.70 (0.20)	0.02 (0.24)	0.78 (0.24)	0.05 (0.19)
Treatment cycle 6‡	0.74 (0.25)	0.05 (0.23)	0.77 (0.17)	0.01 (0.14)
Treatment cycle 7‡	0.69 (0.25)	0.01 (0.29)	0.75 (0.20)	–0.00 (0.16)
Treatment cycle 8‡	0.71 (0.26)	0.00 (0.28)	0.74 (0.27)	–0.01 (0.24)
Treatment cycle 9‡	0.68 (0.34)	–0.04 (0.35)	0.76 (0.16)	0.01 (0.13)
Treatment cycle 10‡	0.68 (0.26)	–0.03 (0.27)	0.81 (0.15)	0.05 (0.17)
Treatment cycle 11‡	0.66 (0.18)	–0.04 (0.27)	0.75 (0.17)	0.01 (0.15)
Treatment cycle 12‡	0.72 (0.19)	–0.01 (0.25)	0.76 (0.19)	0.01 (0.12)
Treatment cycle 13‡	0.72 (0.23)	0.01 (0.25)	0.77 (0.15)	0.02 (0.12)
Treatment cycle 14‡	0.73 (0.23)	0.06 (0.28)	0.80 (0.14)	0.07 (0.14)
EOT§	0.58 (0.33)	–0.12 (0.32)	0.43 (0.29)	–0.28 (0.19)

†A higher score represents a better level of quality of life.
‡At Day 1. §EOT: 30 days after last study treatment administration.
Abbreviations: CFB, change from baseline; EQ-5D-5L, Euro QoL Group self-report questionnaire with 5 dimensions and 5 levels per dimension; EOT, end-of-treatment; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; MM, multiple myeloma; Pd, pomalidomide, low-dose dexamethasone; SD, standard deviation.

Table 25: ICARIA-MM key secondary endpoint – Visual analogue scale – EQ-5D-5L, 4L population

	Pd (N=53)		IsaPd (N=49)	
	Observed score†	CFB	Observed score†	CFB
Baseline, Mean (SD)	64.17 (19.66)	—	68.46 (19.96)	—
Treatment cycle 2§	65.35 (19.45)	0.96 (18.80)	66.64 (19.38)	–1.18 (19.64)
Treatment cycle 3§	69.07 (16.99)	1.90 (19.00)	69.84 (20.77)	1.44 (20.17)
Treatment cycle 4‡	69.08 (16.31)	2.93 (18.95)	70.56 (18.61)	2.07 (18.67)
Treatment cycle 5‡	69.68 (17.21)	4.74 (18.20)	71.39 (14.64)	2.18 (19.26)
Treatment cycle 6‡	68.63 (17.84)	3.22 (17.37)	72.36 (14.23)	2.06 (17.47)
Treatment cycle 7‡	67.00 (16.73)	3.25 (19.72)	76.20 (13.00)	4.40 (16.97)
Treatment cycle 8‡	67.76 (16.23)	0.76 (22.35)	71.03 (18.31)	0.36 (18.67)
Treatment cycle 9‡	68.87 (18.92)	0.17 (22.51)	72.57 (15.38)	0.50 (14.32)
Treatment cycle 10‡	67.29 (16.49)	–0.38 (20.73)	73.21 (14.81)	–1.32 (14.35)
Treatment cycle 11‡	67.26 (16.74)	1.00 (23.04)	74.12 (13.74)	2.08 (15.76)
Treatment cycle 12‡	70.06 (14.34)	1.88 (23.62)	70.76 (14.13)	–3.14 (13.60)
Treatment cycle 13‡	70.07 (12.33)	4.40 (21.50)	70.11 (14.64)	–2.39 (15.49)
Treatment cycle 14‡	71.73 (15.99)	6.36 (23.59)	75.77 (14.37)	2.92 (15.59)
End-of-treatment§, Mean (SD)	58.50 (20.19)	–5.81 (20.63)	50.12 (21.68)	–11.00 (21.32)

†Safety population evaluable for quality of life assessment: patients from the safety population who have completed the baseline and at least 1 post baseline assessment.
‡A higher score represents a better level of quality of life.
§End-of-treatment: 30 days after last study treatment administration.
Abbreviations: CFB, change from baseline; EQ-5D-5L, Euro QoL Group self-report questionnaire with 5 dimensions and 5 levels per dimension; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; MM, multiple myeloma; Pd, pomalidomide, low-dose dexamethasone; SD, standard deviation.

B.2.6.1.6 Efficacy conclusions for study EFC14335 (ICARIA-MM)

ITT population

Primary efficacy endpoint

- Treatment with IsaPd significantly increased PFS (based on IRC assessment) compared with Pd. At the cut-off date, 73 and 89 PFS events had occurred in the IsaPd in Pd arms, respectively. Median PFS was significantly longer in the IsaPd arm (11.53 months [95% CI; 8.936, 13.897]) than in the Pd arm (6.47 months, [95% CI; 4.468, 8.279]), respectively. The stratified HR was 0.596 (95% CI; 0.436, 0.814) characterising a 40.4% risk reduction of disease progression or death with IsaPd compared with Pd. The difference between the two treatments (assessed by means of one-sided stratified log-rank test) was statistically significant in favour of IsaPd, with a p-value of 0.001 which met the pre-specified efficacy boundary of 0.025

- Furthermore, consistent improvement in PFS was demonstrated for IsaPd over Pd across all of the pre-specified patient subgroups, including those poor prognosis (i.e. high-risk cytogenetic population, elderly patients, renal function impairment, heavily pre-treated patients [>3 prior lines], and relapsed/refractory patients)

- The results for sensitivity analyses were consistent with the primary analysis, demonstrating robustness of the results. Investigator-assessed PFS, based on local laboratory M-protein results and Investigator assessment of radiologic imaging, was consistent with the IRC assessment of PFS. Median PFS in the IsaPd arm was 11.14 months (95% CI; 7.491, 14.784) and was longer than compared with 6.54 months (4.468 to 7.885) in the Pd arm (HR=0.602; p=0.0009)

- The HR for PFS, adjusted in multivariate analyses for demographic and baseline characteristics, was 0.484 (95% CI; 0.334, 0.702). This lower value for the adjusted HR, compared with that of the primary analysis of PFS (HR=0.596 [95% CI; 0.436, 0.814]), provides further evidence of the robustness of the primary analysis results and suggests there may have been some confounding factors among the analysed covariates that influenced the treatment effect in the primary analysis in favour of the Pd arm.

Key secondary endpoints

- A statistically significant improvement in ORR was shown in patients who received IsaPd compared with Pd (60.4% vs 35.3%; p<0.0001). A consistent improvement in ORR was observed across the pre-specified subgroups

- At a median duration of follow-up (11.56 and 11.73 months in the IsaPd and Pd arms, respectively), a trend toward longer OS was observed in patients who received IsaPd compared with Pd (HR=0.687; [95% CI; 0.461, 1.023]), but median OS had not been reached in either treatment arm. At the time of the analysis, the probability of surviving 12 months was 0.720 (95% CI; 0.636, 0.787) in the IsaPd arm and 0.633 (95% CI; 0.545, 0.709) in the Pd arm. Further follow-up is ongoing

Other secondary endpoints

- Treatment with IsaPd improved median time to progression (12.71 months in IsaPd arm vs 7.75 months in Pd arm)

- Duration of response was longer with IsaPd than with Pd treatment (13.27 months vs 11.07 months)

- Responses in the IsaPd arm occurred more rapidly, with the median time to first response 1.94 months and 3.02 months in the IsaPd and Pd arms, respectively

- Among patients in the high-risk cytogenetic population, IsaPd improved median PFS based on the IRC assessment (7.491 vs 3.745 months). The stratified HR was 0.655 (95% CI; 0.334, 1.283), corresponding to a reduction of 34.5% in the risk of progression or death with IsaPd compared with Pd

- The incidence of MRD negativity at the sensitivity level of 10-5 was greater in patients who received IsaPd (8 patients, 5.2%) compared with Pd (0 patients)

Patients at 4L of treatment

Primary efficacy endpoint

- Treatment with IsaPd substantially improved PFS (based on IRC assessment) in the 4L population, compared with Pd. At the cut-off date, a total of 29 (55.8%) and 25 (43.1%) of the 4L patients in the IsaPd and Pd arms, respectively, had not had a PFS event and were censored. Median PFS was significantly longer in the IsaPd arm (13.31 months [95% CI; 7.425, not calculable (NC)]) than in the Pd arm ((7.82 months [95% CI; 4.468, 11.072]). The stratified HR was 0.598 (95% CI; 0.348, 1.030) representing a 40.2% risk reduction of disease progression or death in favour of IsaPd vs Pd

Key secondary endpoints

- At the cut-off date, a total of 34 deaths were reported among patients in 4L of treatment (11 in IsaPd arm and 23 in Pd arm). Although OS was considered immature at this stage, a trend towards longer OS in IsaPd (vs Pd) was observed (HR of 0.494; [95% CI; 0.240, 1.015]), with a median OS of 14.36 months in the Pd arm while in the IsaPd it had not been reached

- IsaPd demonstrated a strong favourable trend in OS despite the extensive use of novel agents, such as daratumumab, post progression in the Pd arm and the high level of censoring (10.0% in IsaPd vs 54.2% in Pd)

- ORR for patients in 4L, was numerically better in the IsaPd arm than in the Pd arm (53.8% vs 46.6%; p=0.3991)
- Quality-of-life as measured by EORTC-QLQ-C30 GHS score was sustained over time and similar in both treatment groups, in patients 4L of treatment

Other secondary endpoints

- Treatment with IsaPd improved median time to progression (13.31 months in IsaPd arm vs 8.05 months in Pd arm)

- Responses in the IsaPd arm occurred more rapidly, with the median time to first response 1.91 months and 3.02 months in the IsaPd and Pd arms, respectively

- Among patients in the high-risk cytogenetic population, IsaPd improved median PFS based on the IRC assessment (7.031 vs 2.825 months). The stratified HR was 0.683 (95% CI; 0.222, 2.102), corresponding to a reduction of 31.7% in the risk of progression or death with IsaPd compared with Pd

- The incidence of MRD negativity at the sensitivity level of 10^{-5} was greater in patients who received IsaPd (8 patients, 7.7%) compared with Pd (0 patients)

B.2.7 *Subgroup analysis*

Subgroup analyses of the results obtained in the primary analysis of the assessed outcomes were conducted using the pre-planned subgroups presented in Table 6; the methodology used for the subgroup analysis is presented in Table 10. The results for the pre-planned subgroup analysis of the primary outcome – progression free survival (PFS) – are presented in Section B.2.6.1.1.

Post-hoc analyses of relevant clinical outcomes for a subgroup of patients in the ICARI−MM trial at 4L of treatment, were conducted to inform the economic model. Results are presented in Section B.2.6.1.

B.2.8 *Study TCD14079 (Phase Ib, NCT02283775)*

Study TCD14079 was a Phase Ib, multicentre, open-label, non-comparative, dose-escalation study, conducted to determine the safety and recommended dose of isatuximab in combination with pomalidomide/dexamethasone, in patients with RRMM (68, 69). This study was not used to inform the economic model or the ITC as it was not a randomised controlled trial. Nevertheless, it is presented here as a supportive study, to demonstrate the clinical activity and the manageable safety profile of isatuximab plus pomalidomide and dexamethasone, in heavily pre-treated patients with RRMM. The methods and results for this trial are summarised in Table 26 (full details in Appendix M.1).

Table 26: Summary of Phase Ib study TCD14079

Study objective	**Primary objective (Part A)** To determine the safety and recommended dose of isatuximab (5, 10, or 20 mg/kg) in combination with standard doses of pomalidomide (4 mg) and dexamethasone (40 mg) **Secondary objectives (Part B)** To evaluate the pharmacokinetics, immunogenicity, and efficacy of isatuximab (5, 10, or 20 mg/kg) in combination with standard doses of pomalidomide (4 mg) and dexamethasone (40 mg)
Trial design	Phase Ib, multicentre, open-label, non-comparative, dose-escalation study of isatuximab in combination with standard doses of pomalidomide/dexamethasone in patients with RRMM. After completion of the dose-escalation phase, additional patients were enrolled and treated at the recommended dose in an expansion cohort
Key findings	• One DLT was reported at each dose level; none of these led to treatment discontinuation, and all resolved with dose omission or reduction • MTD was not reached in the dose-escalation cohort • The most common AEs included fatigue (62%), URT infection (42%), IR (42%), and dyspnoea (40%) • The most common grade ≥3 TEAE was pneumonia (17.8%) • Haematologic laboratory abnormalities were common: lymphopenia, leukopenia, anaemia (98% each), neutropenia (93%) and thrombocytopenia (84%) • Median treatment duration was 9.6 months • At a median overall follow-up duration of 8.6 months, the ORR was 62% • The CBR was 73%

	• Median DOR was 18.7 months • Median PFS was 17.6 months
Conclusions	• In Study TCD14079, isatuximab combined with standard doses of pomalidomide/dexamethasone was well tolerated with promising clinical activity, in heavily pre-treated patients with RRMM • Isatuximab at 10 mg/kg (four initial QW IV infusions followed by Q2W IV infusions) was selected for use in the Phase III RCT ICARIA-MM (Study EFC14335)

Abbreviations: AEs, adverse events; CBR, clinical benefit rate; DLT, dose-limiting toxicity; DOR, duration of response; IR, infusion reactions; IV, intravenous; MM, multiple myeloma; MTD, maximum tolerated dose; ORR, overall response rate; PFS, progression-free survival; QW, weekly; Q2W, every two weeks; RCT, randomised controlled trial; RRMM, relapsed or refractory multiple myeloma, TEAEs, treatment-emergent adverse events; URT, upper respiratory tract.

B.2.9 *Meta-analysis*

Only one relevant RCT evaluating isatuximab+pomalidomide+dexamethasone was identified and therefore no meta-analysis was performed.

B.2.10 *Indirect and mixed treatment comparisons*

As noted above, PanVd is not a relevant comparator to IsaPd. To meet requirements of the NICE scope an indirect comparison and MAIC was performed to inform an economic comparison to IsaPd. Full details of these are presented in Appendix K.

B.2.11 *Adverse reactions*

B.2.11.1 *Studies reported in Section 2.2*

The cut-off date for the safety analyses was 22nd November 2018.

Key safety evidence provided by the pivotal Phase III Study EFC14335 (ICARIA-MM) for all patients, is presented below. Additional safety outcomes are presented in Appendix G.

B.2.11.1.1 Overview of treatment-emergent adverse events (TEAEs)

ICARIA-MM – ITT population

At least one TEAE was reported in almost all the patients in both arms (99.3% and 98.0% in the IsaPd and Pd arms, respectively). While grade 3–4 TEAEs were reported more frequently in the IsaPd arm than in the Pd arm (84.9% vs 69.1%), the incidence of grade 5 (fatal) TEAEs was slightly lower in the IsaPd arm in comparison with the Pd arm (7.9% vs 9.4%) (Table 27). Grade ≥3 treatment related TEAEs were reported more frequently in the IsaPd than in the Pd arm (71.7% vs 47.7%). A higher incidence of serious TEAEs was observed in the IsaPd arm than in the Pd arm (61.8% vs 53.7%). However, after adjustment for the longer treatment duration in the IsaPd arm, the treatment emergent SAE incidence rates were similar in the IsaPd and Pd arms (1.36 and 1.30 incidence rate per patient year, respectively). Definitive treatment discontinuation due to TEAEs occurred more frequently in the Pd vs the IsaPd arm (12.8% vs 7.2%). Isatuximab was selectively discontinued in four patients (2.6%) in the IsaPd arm.

Table 27: ICARIA-MM safety outcomes – TEAEs – overview (safety population)

Event n (%)	Pd (N=149)	IsaPd (N=152)
Patients with any TEAE	146 (98.0)	151 (99.3)
Patients with any grade ≥3 TEAE	105 (70.5)	132 (86.8)
Patients with any grade 3–4 TEAE	103 (69.1)	129 (84.9)
Patients with any grade 5 TEAE	14 (9.4)	12 (7.9)
Patients with any treatment emergent SAE[†]	80 (53.7)	94 (61.8)
Patients with any TEAE leading to definitive treatment discontinuation	19 (12.8)	11 (7.2)
Patients with any TEAE leading to premature discontinuation of isatuximab	N/A	4 (2.6)
Patients with any TEAE leading to premature discontinuation of pomalidomide	0	8 (5.3)
Patients with any TEAE leading to premature discontinuation of dexamethasone	2 (1.3)	2 (1.3)
Patients with any AESI[‡]	1 (0.7)	10 (6.6)
Patients with any IR of grade ≥3	0	4 (2.6)
Patients with any treatment related TEAE[δ]	119 (79.9)	138 (90.8)
Patients with any treatment-related grade ≥3 TEAE	71 (47.7)	109 (71.7)
Patients with any serious[¶] treatment related TEAE	24 (16.1)	54 (35.5)

†TEAEs with a start date before the operational cut-off date and becoming serious after the operational cut-off date were excluded from this analysis. ‡AESI include IR of grade 3 or 4, pregnancy, overdose and second primary malignancy. §Treatment-related TEAEs are TEAEs related to at least one drug of the combination. ¶TEAEs with a start date before the operational cut-off date and becoming serious after the operational cut-off date were excluded from this analysis.
Abbreviations: AESI, adverse event of special interest; IR; infusion reaction; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; MM, multiple myeloma; N/n, number of patients; N/A: not applicable; Pd, pomalidomide, low-dose dexamethasone; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

ICARIA-MM – Patients at 4L of treatment

A post-hoc analysis of the safety data set for ICARIA-MM patients at 4L of treatment was conducted to inform the economic model.

An overview of the reported treatment-emergent adverse events (TEAE) for patients at 4L of treatment in the ICARIA-MM trial, is presented in Table 28. The proportion of patients experiencing any grade TEAE was comparable between both treatment arms (100% in the IsaPd and 98.3% in the Pd arm). Grade ≥3 TEAEs were reported more frequently in the IsaPd arm than in the Pd arm (84.3% vs 69.0%). A higher proportion of patients in the IsaPd reported treatment-emergent serious adverse events (SAE) in

comparison with the Pd arm (64.7% vs 53.4%). Nevertheless, fewer patients in the IsaPd arm (vs Pd arm) had fatal events (7.8% vs 8.6%) or had to definitively discontinue treatment due to any TEAE (7.2% vs 17.2%). Isatuximab was selectively discontinued in only one patient (2.0%) in the IsaPd arm. Grade ≥3 infusion reactions (IR) occurred in only one patient (2.0%) in the IsaPd arm, and all IR were resolved by the time of the cut-off date.

Table 28: ICARIA-MM safety outcomes – TEAEs[†] – overview, 4L (safety population)

n (%)	Pd (N=58)	IsaPd (N=52)
Patients with any TEAE	57 (98.3)	51 (100)
Patients with any grade ≥3 TEAE	40 (69.0)	43 (84.3)
Patients with any grade 3–4 TEAE	39 (67.2)	42 (82.4)
Patients with any grade 5 TEAE	5 (8.6)	4 (7.8)
Patients with any treatment emergent SAE[†]	31 (53.4)	33 (64.7)
Patients with any TEAE leading to definitive treatment discontinuation	10 (17.2)	4 (7.8)
Patients with any TEAE leading to premature discontinuation of isatuximab	N/A	1 (2.0)
Patients with any TEAE leading to premature discontinuation of pomalidomide	0	2 (3.9)
Patients with any TEAE leading to premature discontinuation of dexamethasone	1 (1.7)	1 (2.0)
Patients with any AESI[‡]	0	4 (7.8)
Patients with any IR of grade ≥3	0	1 (2.0)
Patients with any treatment related TEAE[δ]	45 (77.6)	45 (88.2)
Patients with any treatment-related grade ≥3 TEAE	27 (46.6)	33 (64.7)
Patients with any serious[¶] treatment related TEAE	11 (19.0)	17 (33.3)

†Cut-off date: 22nd November 2018. ‡TEAEs with a start date before the operational cut-off date and becoming serious after the operational cut-off date were excluded from this analysis.
Abbreviations: AESI, adverse event of special interest; IR; infusion reaction; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; MM, multiple myeloma; N/n, number of patients; N/A: not applicable; Pd, pomalidomide, low-dose dexamethasone; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

B.2.11.1.2 TEAEs by primary System Organ Class (SOC) and preferred term (PT)

A summary of all grade TEAEs by primary System Organ Class (SOC) and preferred term (PT) is presented in Table 29.

Treatment-emergent AEs reported at a ≥25% incidence and ≥5% more frequently in the IsaPd than in the Pd arm were in the SOCs of infections and infestations (80.9% and 64.4% in the IsaPd and Pd arms, respectively), blood and lymphatic system disorders (58.6% and 43.6%), musculoskeletal and connective tissue disorders (56.6% and 49.7%), injury, poisoning and procedural complications (47.4% and 11.4%), nervous system disorders (40.8% and 28.9%), and respiratory, thoracic and mediastinal disorders (40.8% and 32.2%).

Treatment-emergent AEs reported in ≥10% of patients in either treatment group were neutropenia (46.7% and 33.6% in the IsaPd and Pd arms, respectively), infusion related reaction (36.8% and 1.3%), upper respiratory tract infection (28.3% and 17.4%), diarrhoea (25.7% and 19.5%), bronchitis (23.7% and 8.7%), pneumonia (20.4% and 17.4%), fatigue (17.1% and 21.5%), back pain (16.4% and 14.8%), constipation (15.8% and 17.4%), dyspnoea (15.1% and 10.1%), asthenia (15.1% and 18.1%), nausea (15.1% and 9.4%), pyrexia (14.5% and 14.1%), peripheral oedema (13.2% and 10.7%), thrombocytopenia (12.5% and 12.1%), febrile neutropenia (11.8% and 2.0%), vomiting (11.8% and 3.4%), arthralgia (10.5% and 8.7%), and muscle spasms (9.2% and 10.1%).

The incidence of cardiac disorders was higher in the IsaPd arm than in the Pd arm (14.5% vs 4.0%), mostly due to more cardiac arrhythmias HLGT in the IsaPd arm (11.2% and 2.0% in the IsaPd and Pd arms, respectively). Most of the cardiac arrhythmias were Grade 1 or 2 (7.9% and 2.0% of patients in the IsaPd and Pd arms, respectively), with Grade ≥3 TEAEs in 3.3% and 0.7% of patients in the IsaPd and Pd arms, respectively. The most frequent cardiac arrhythmias were atrial fibrillation, 7 (4.6%) patients in IsaPd and 3 (2.0%) in Pd arm all grades and 3 (2.0%) in IsaPd arm and 1 (0.7%) in Pd arm Grade ≥3.

Nervous system disorders were reported more frequently in the IsaPd arm (40.8%, Grade ≥3: 7.9%) than in the Pd arm (28.9%, Grade ≥3: 5.4%). The TEAEs reported in ≥3% of patients in the IsaPd arm were headache (9.9% and 5.4% in the IsaPd and Pd arms, respectively), tremor (7.9% and 4.0%), peripheral sensory neuropathy (7.2% and 6.0%), dizziness (5.3% and 2.7%), and syncope (3.9% and 2.0%).

Renal and urinary disorders were reported in 11.8% of patients in the IsaPd arm and 15.4% of patients in the Pd arm, with acute kidney injury as the most commonly reported TEAE (4.6% and 5.4%) among these.

Skeletal-related TEAEs were reported at a similar incidence in the two treatment arms; these included pathological fracture (5.9% and 5.4% in the IsaPd and Pd arms, respectively), traumatic fracture (3.3% and 0.7%), and osteoporotic fracture (0.7% and 0%).

Thromboembolic TEAEs were reported at a similar incidence in the two treatment arms: 5.3% in the IsaPd arm (Grade ≥3: 2.6%) and 4.7% in the Pd arm (Grade ≥3: 2.7%).

Infusion related reactions were reported in two patients in the Pd arm; after discontinuing the study treatment (Pd), both these patients went on to receive post-treatment therapy with daratumumab, and both developed IRs attributed to daratumumab, within 30 days from the last dose of study treatment.

Table 29: ICARIA-MM safety outcomes –TEAEs[†] by SOC and PT[‡] (safety population)

Event n (%)[δ]	Pd (N=149)		IsaPd (N=152)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any class	146 (98.0)	105 (70.5)	151 (99.3)	132 (86.8)
Infections and infestations	96 (64.4)	45 (30.2)	123 (80.9)	65 (42.8)
Upper respiratory tract infection	26 (17.4)	1 (0.7)	43 (28.3)	5 (3.3)
Bronchitis	13 (8.7)	1 (0.7)	36 (23.7)	5 (3.3)
Pneumonia	26 (17.4)	23 (15.4)	31 (20.4)	25 (16.4)
Urinary tract infection	14 (9.4)	2 (1.3)	15 (9.9)	7 (4.6)
Nasopharyngitis	7 (4.7)	0	14 (9.2)	0
Influenza	8 (5.4)	1 (0.7)	9 (5.9)	4 (2.6)
Lower respiratory tract infection	8 (5.4)	4 (2.7)	8 (5.3)	5 (3.3)
Blood and lymphatic system disorders	65 (43.6)	60 (40.3)	89 (58.6)	87 (57.2)
Neutropenia	50 (33.6)	48 (32.2)	71 (46.7)	70 (46.1)
Thrombocytopenia	18 (12.1)	18 (12.1)	19 (12.5)	18 (11.8)
Febrile neutropenia	3 (2.0)	3 (2.0)	18 (11.8)	18 (11.8)
Metabolism and nutrition disorders	20 (13.4)	8 (5.4)	28 (18.4)	13 (8.6)
Decreased appetite	7 (4.7)	1 (0.7)	15 (9.9)	2 (1.3)
Psychiatric disorders	29 (19.5)	4 (2.7)	26 (17.1)	4 (2.6)
Insomnia	12 (8.1)	1 (0.7)	13 (8.6)	1 (0.7)
Nervous system disorders	43 (28.9)	8 (5.4)	62 (40.8)	12 (7.9)
Headache	8 (5.4)	0	15 (9.9)	0
Tremor	6 (4.0)	0	12 (7.9)	3 (2.0)
Peripheral sensory neuropathy	9 (6.0)	0	11 (7.2)	1 (0.7)
Dizziness	4 (2.7)	0	8 (5.3)	0
Vascular disorders	17 (11.4)	6 (4.0)	23 (15.1)	4 (2.6)
Hypertension	8 (5.4)	3 (2.0)	7 (4.6)	2 (1.3)
Respiratory, thoracic and mediastinal disorders	48 (32.2)	10 (6.7)	62 (40.8)	14 (9.2)
Dyspnoea	15 (10.1)	2 (1.3)	23 (15.1)	6 (3.9)
Cough	11 (7.4)	1 (0.7)	14 (9.2)	0
Oropharyngeal pain	3 (2.0)	0	8 (5.3)	0
Gastrointestinal disorders	74 (49.7)	3 (2.0)	81 (53.3)	9 (5.9)
Diarrhoea	29 (19.5)	1 (0.7)	39 (25.7)	3 (2.0)
Constipation	26 (17.4)	0	24 (15.8)	0
Nausea	14 (9.4)	0	23 (15.1)	0
Vomiting	5 (3.4)	0	18 (11.8)	2 (1.3)
Stomatitis	4 (2.7)	0	10 (6.6)	1 (0.7)

Event n (%)[δ]	Pd (N=149)		IsaPd (N=152)	
Skin and subcutaneous tissue disorders	36 (24.2)	0	39 (25.7)	2 (1.3)
Pruritus	9 (6.0)	0	5 (3.3)	0
Rash	8 (5.4)	0	5 (3.3)	0
Musculoskeletal and connective tissue disorders	74 (49.7)	8 (5.4)	86 (56.6)	12 (7.9)
Back pain	22 (14.8)	2 (1.3)	25 (16.4)	3 (2.0)
Arthralgia	13 (8.7)	1 (0.7)	16 (10.5)	4 (2.6)
Muscle spasms	15 (10.1)	0	14 (9.2)	0
Musculoskeletal chest pain	7 (4.7)	0	13 (8.6)	0
Bone pain	8 (5.4)	2 (1.3)	12 (7.9)	1 (0.7)
Muscular weakness	7 (4.7)	0	11 (7.2)	1 (0.7)
Myalgia	5 (3.4)	0	10 (6.6)	0
Pathological fracture	8 (5.4)	3 (2.0)	9 (5.9)	3 (2.0)
Renal and urinary disorders	23 (15.4)	12 (8.1)	18 (11.8)	9 (5.9)
Acute kidney injury	8 (5.4)	6 (4.0)	7 (4.6)	4 (2.6)
General disorders and administration site conditions	89 (59.7)	18 (12.1)	82 (53.9)	23 (15.1)
Fatigue	32 (21.5)	0	26 (17.1)	6 (3.9)
Asthenia	27 (18.1)	4 (2.7)	23 (15.1)	5 (3.3)
Pyrexia	21 (14.1)	2 (1.3)	22 (14.5)	2 (1.3)
Oedema peripheral	16 (10.7)	0	20 (13.2)	1 (0.7)
Disease progression	8 (5.4)	8 (5.4)	8 (5.3)	8 (5.3)
Investigations	10 (6.7)	2 (1.3)	17 (11.2)	5 (3.3)
Weight decreased	2 (1.3)	0	10 (6.6)	0
Injury, poisoning and procedural complications	17 (11.4)	1 (0.7)	72 (47.4)	8 (5.3)
Infusion related reaction	2 (1.3)	0	56 (36.8)	4 (2.6)
Fall	8 (5.4)	1 (0.7)	8 (5.3)	0

†Only SOC with at least one PT ≥5% in at least one treatment group. ‡According to MedDRA 21.0. δNumber and percentage of patients with at least one TEAE.
Note: Table sorted by SOC internationally agreed order and by decreasing frequency of PT for all grades in IsaPd group.
Abbreviations: IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; MedDRA, Medical Dictionary for Regulatory Activities; MM, multiple myeloma; N/n, number of patients; Pd, pomalidomide, low-dose dexamethasone; PT, preferred term; SOC, System Organ Class; TEAE, treatment-emergent adverse event.

Infusion reactions

A summary of the reported infusion reactions (IR) is presented in Table 30.

Infusion reactions were reported in 58 (38.2%) patients in the IsaPd arm. Most of the patients had IRs that were Grade 1 (3.9%) or Grade 2 (31.6%); 1.3% of patients had Grade 3 and 1.3% had Grade 4 IRs and there were no Grade 5 (fatal) IRs. The majority of patients with IRs had a single episode, with 6 (3.9%) patients having 2 episodes; 1 of the 6 patients had 2 episodes at the same infusion and no patient had 3 or more episodes. All 58 patients with IRs had their first onset during the first infusion, with 2.0% and 1.3% of patients also having IRs at their second and fourth infusions, respectively. No IRs occurred after the fourth infusion. All IRs occurred on the same day of the infusion. In most cases, the IRs were managed with infusion interruption (44 patients) and/or medication (49 patients). Discontinuation of isatuximab occurred in 4 (2.6%) patients, who continued treatment with Pd as per protocol; 28.9% of patients had dose interrupted due to the IR, 6.6% of patients did not require any action taken with isatuximab, and no patient definitively discontinued IsaPd treatment due to an IR. All the IRs resolved without sequelae on the same day (98.4%) or by the next day (1.6%).

Table 30: ICARIA-MM safety outcomes – IR (safety population)

	IsaPd (N=152)
Patients with at least one IR, n (%)	58 (38.2)
Worst grade of IR, n (%)	
Grade 1	6 (3.9)
Grade 2	48 (31.6)
Grade 3	2 (1.3)
Grade 4	2 (1.3)
Action taken with isatuximab by patient, n (%)	
Dose not changed	10 (6.6)
Drug interrupted	44 (28.9)
Drug withdrawn	4 (2.6)
Corrective treatment given, n (%)	49 (32.2)
Episodes by patient, n (%)	
1	52 (34.2)
≥1	58 (38.2)
≥2	6 (3.9)
Onset of IR at first infusion	58 (38.2)
Onset of IR leading to drug withdrawal at	
First infusion	3 (2.0)
Subsequent infusions	1 (0.7)

	IsaPd (N=152)
Total number of IR episodes, n	64
Grade of IR, n (%)	
Grade 1	6 (9.4)
Grade 2	54 (84.4)
Grade 3	2 (3.1)
Grade 4	2 (3.1)
Grade 5	0
Day of IR onset, n (%)	
Infusion day	64 (100)
IR duration	
1 day	63 (98.4)
2 days	1 (1.6)
Not recovered	0

Abbreviations: IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; IR, infusion reaction; MM, multiple myeloma.

B.2.11.2 *Additional studies*

The clinical systematic review, detailed in Section B.2.1, also included adverse events, and did not identify any additional studies.

B.2.11.3 *Safety overview*

Overall, the available data show that treatment with IsaPd was associated with a manageable safety profile. Treatment duration in the IsaPd arm was longer than with Pd (median: 41 weeks vs 24 weeks), reflecting the prolonged disease control in the IsaPd arm. Nearly twice as many patients were still on treatment at the data cut-off (42.2% and 22.9% in the IsaPd and Pd arms respectively).

Isatuximab IRs occurred in 38.2% of patients (predominantly Grade 1-2; Grade 1-2: 35.5%, Grade 3: 2.6%), with onset at first infusion. All infusion reactions were reversible. During treatment, Grade 3-4 neutropenia occurred more frequently in the IsaPd arm overall, with a greater incidence of Grade 4 in the IsaPd arm (60.5% vs 30.9%). The median time to onset of Grade 3-4 neutropenia was 21 and 22 days in the IsaPd and Pd arms, respectively. Febrile neutropenia occurred as a TEAE at a higher incidence in the IsaPd arm compared with the Pd arm (11.8% vs 2.0%) as did neutropenic infection (25.0% vs 19.5%).

Other than infusion reactions and neutropenia, the TEAEs reported most frequently and at a higher incidence in the IsaPd arm than the Pd arm were upper respiratory tract infection (28.3% vs 17.4%), diarrhoea (25.7% vs 19.5%), bronchitis (23.7% vs 8.7%), and pneumonia (20.4% vs 17.4%). The incidence and severity of lower respiratory TEAEs in the IsaPd arm (36.8%) was higher compared with the Pd arm (25.5%) and the most frequent event was dyspnoea (15.1% and 10.1% in the IsaPd and Pd arms,

respectively). Infusion-related reactions were reported in 38.2% of patients in the IsaPd arm and the majority were Grade 1-2 (Grade 1-2: 35.5%, Grade 3: 2. %).

The incidence of cardiac disorders was higher in the IsaPd arm than in the Pd arm (14.5% vs 4.0%), mostly due to more cardiac arrhythmias in the IsaPd arm (11.2% and 2.0% in the IsaPd and Pd arms, respectively). Atrial fibrillation was reported in 7 (4.6%) patients in IsaPd arm and 3 (2.0%) patients in Pd arm.

In the IsaPd and Pd arms, 86.8% and 70.5% patients, respectively, had Grade ≥3 TEAEs, most frequently neutropenia (46.1% and 32.2% in the IsaPd and Pd arms, respectively), pneumonia (16.4% and 15.4%), thrombocytopenia (11.8% and 12.1%), and febrile neutropenia (11.8% and 2.0%).

Serious TEAEs were reported more frequently in patients receiving IsaPd compared with Pd (61.8% vs 53.7%). However, exposure-adjusted incidence rates of serious TEAEs were similar in both arms (1.36 and 1.30 incidence rate per patient year). The most common serious TEAEs were pneumonia (15.1% and 15.4% of patients in the IsaPd and Pd arms, respectively), and febrile neutropenia (6.6% and 2.0%). Treatment with IsaPd did not lead to an increase in fatal TEAEs (7.9% in the IsaPd arm and 9.4% in the Pd arm). Definitive treatment discontinuation due to TEAEs occurred infrequently and at a similar rate in both treatment arms (7.2% in the IsaPd arm and 12.8% in the Pd arm).

B.2.12 *Ongoing studies*

The IKEMA study, a multinational clinical study comparing isatuximab, carfilzomib and dexamethasone with carfilzomib and dexamethasone in patients with relapsed and/or refractory multiple myeloma, is currently ongoing. Results are expected around the middle of 2020.

B.2.13 *Innovation*

Isatuximab in combination with pomalidomide and dexamethasone represents a step-change in the management of patients who have received 3 prior lines of treatment, including lenalidomide. In the first well-controlled, international, randomised Phase 3 trial of a triplet regimen based on pomalidomide and dexamethasone in patients with RRMM treated with at least 2 prior lines, the addition of isatuximab to Pd led to clinically meaningful improvement in PFS and OS as compared with Pd.

In a subgroup of heavily pre-treated patients receiving IsaPd as 4L treatment, patients on IsaPd had a median PFS of 13.3 months, compared with 7.8 months on Pd. Median OS was not reached in the IsaPd arm, but patients on Pd had a median OS of 14.4 months. These results should be interpreted in the context of nearly 79% of patients in the IsaPd arm and 60% in the Pd arm still being alive at the 1-year follow-up. At this stage of the treatment pathway, when patients often lose hope at relapse, the potential for additional treatment options to extend the treatment pathway would be valuable to patients and their families. In previous appraisals, patient experts explained the physical and psychological value of PFS for patients. Furthermore, clinical experts explained that PFS is an important outcome to patients as MM can be fatal, particularly in older people.

In comparison with current treatment options for this patient population, isatuximab, in combination with pomalidomide and dexamethasone, has demonstrated unprecedented progression-free survival in patients who have received at least 3 prior lines of treatment, including lenalidomide (Table 31).

Table 31: PFS and OS in patients who received 3 prior lines of treatment

Treatment	IsaPd	Pd	Pd	Pd	Pd	Pd	DARA		
Source	ICARIA-MM		**RWE[1]**	**RWE[2]**	**RWE[3]**	**MM-003**	**SIRIUS**	**RWE[4]**	**RWE[5]**
% prior lenalidomide	**92.3%**	**87.9%**	**100%**	**87%**	**100%**	**94.7%**	**99%**	**NR**	**93.8%**
Median number of prior lines/therapies	**3**	**3**	**3**	**4**	**4**	**5**	**5**	**3**	**3**
Median PFS (months)	13.3	7.8	3.4	8.0	4.3	4.0	4.0	4.9	3
Median OS (months)	33.3†	14.4	10.9	8.6	13.7	13.1	20.1	NR	NR

†Predicted outcomes based on CEM model.
RWE[1], real world evidence UK study, Miles & Wells 2015 (70); RWE[2], real world evidence study reported in TA427 (conducted by Celgene) (40); RWE[3] – real world evidence study in UK by Maciocia 2015 (71); TA510 (41), RWE[4] real-world evidence study by Sparksman 2019 (72), RWE[5] real world evidence study by Taube et al 2019 (73)
Abbreviations: CEM, cost-effectiveness model; DARA, daratumumab monotherapy; IsaPd, isatuximab+ pomalidomide+ dexamethasone; Pd, pomalidomide+ dexamethasone, NR; not reported; RWE, real-world evidence.

Isatuximab has been granted orphan designation from the Committee for Orphan Medicinal Products (COMP). As part of an application to the MHRA for an Early Access to Medicines Scheme (EAMS), isatuximab in combination with pomalidomide and dexamethasone was awarded a 'Promising Innovative Medicine' status in May 2019, the first treatment in RRMM with this award. The panel agreed that the following three criteria were met:

- MM is life-threatening, existing management strategies have serious limitations, and there is therefore a high unmet need
- Isatuximab is likely to offer a major advantage over methods currently used in the UK, based on the available clinical evidence and indirect treatment comparison
- The potential adverse effects of isatuximab are likely to be outweighed by the benefits, allowing for the reasonable expectation of a positive benefit/risk balance; isatuximab has shown promising efficacy outcomes and is associated with a manageable adverse event profile

If successful, the EAMS scheme is expected to start in December 2019.

B.2.14 *Interpretation of clinical effectiveness and safety evidence*

B.2.14.1 *Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology*

At the time of the study cut-off date (median follow-up time was 11.56 months in the IsaPd arm and 11.73 months in the Pd arm of the ICARIA-MM trial), the median OS had not been reached in the ITT population but a trend towards OS improvement for IsaPd vs Pd can be observed (HR 0.687 [95% CI; 0.461, 1.023]). These results should be viewed in light of the number of deaths and the level of censoring. At this time, 34 patients out of 110 (31%) had died (11 in the IsaPd arm and 23 in the Pd arm), resulting in 60.3% censored in the Pd arm and 78.8% in the IsaPd arm. The addition of isatuximab to Pd significantly improved PFS (one-sided p=0.001, meeting the pre-specified efficacy boundary of 0.025) vs Pd alone. Median PFS was significantly prolonged in the IsaPd arm (11.53 months [95% CI; 8.936, 13.897]) in comparison with the Pd arm (6.47 months [95% CI; 4.468, 8.279]). The stratified HR was 0.596 (95% CI; 0.436, 0.814) representing a 40.4% risk reduction of disease progression or death in favour of IsaPd over Pd.

In its expected place in therapy for patients who received 3 prior lines of treatment, 43.1% of patient on Pd and 55.8% on IsaPd were censored in terms of PFS at the time of cut-off. This means that 56.9% of patients on Pd had progressed and 44.2% on IsaPd had progressed. Despite this, the median PFS was prolonged in the IsaPd arm (13.31 months [95% CI; 7.425, NC]) in comparison with the Pd arm (7.82 months [95% CI; 4.468, 11.072]). The stratified hazard ratio was 0.598 (95% CI; 0.348, 1.030) representing a 40.2% risk reduction of disease progression or death in favour of IsaPd over Pd.

Although OS was considered immature at this stage in this subgroup of patients, a trend towards longer OS in the IsaPd arm (vs Pd) was observed (HR of 0.494; [95% CI; 0.240, 1.015]), with a median OS of 14.36 months in the Pd arm, while OS in the IsaPd it had not been reached. It is important to highlight that this strong favourable trend towards longer OS was seen despite the extensive use of novel agents, such as DARA, post progression in the Pd arm. As for the overall population in the ICARIA-MM trial, patients in the 4L of treatment were censored when information on time-to-event was not available due to non-occurrence of the outcome event before the end-of-trial. At the cut-off date, a total of 41 (78.8%) and 35 (60.3%) patients in the IsaPd and Pd arms, respectively, were still alive and were, consequently, censored. This means that, for the analysis of OS in the 4L population, data were available for only 21−40% of patients, reflecting a high level of censoring. It is important to highlight that IsaPd demonstrated this strong favourable trend towards longer OS despite the extensive use of novel agents, such as daratumumab, post progression in the Pd arm.

As a triplet combination that includes IV treatment, IsaPd demonstrated comparable, in some cases better, QoL profile (as assessed by means of EORTC QLQ-C30, QLQ-MY20 and EQ-5D-5L) than doublet oral treatment Pd.

The safety profile of IsaPd is manageable. Compared with Pd alone, mainly upper respiratory tract infection (28.3% vs 17.4%), diarrhoea (25.7% vs 19.5%), bronchitis

(23.7% vs 8.7%), cardiac disorders (14.5% vs 4.0%), and febrile neutropenia (11.8% vs 2.0%) were reported more frequently with IsaPd. However, median treatment duration with IsaPd was considerably longer than with Pd (41 weeks vs 24 weeks). Definitive treatment discontinuation due to TEAEs was more frequent with Pd compared with IsaPd (12.8% vs 7.2%). Withdrawals due to progressive disease were also more frequent with Pd vs IsaPd (59% vs 43%).

Another benefit of IsaPd is that treatment with IsaPd requires shorter infusion times than treatment with daratumumab. In the ICARIA-MM study, mean duration of the first and subsequent infusions were 3.7 and 2.8 hours, respectively. In contrast, DARA has been reported to require infusion times of 8.2 and 3.9 hours for first and subsequent infusions (74-77).

Despite the high level of censoring, the clinical outcomes reported in ICARIA-MM demonstrated the clinical efficacy and safety of isatuximab in combination with pomalidomide and dexamethasone. The censoring does make isatuximab a candidate for CDF where additional data can be collected specific to the UK treated patients.

B.2.14.2 *Strengths and limitations of the clinical evidence base for the technology*

ICARIA-MM is a robustly designed randomised clinical trial, including a population that closely reflects the real-world patient population eligible for treatment with isatuximab, in line with the licensed indication. The data are limited by the fact that OS data are not yet mature, and ICARIA-MM is currently the only RCT available evaluating isatuximab in RRMM.

The ICARIA-MM trial addresses the decision problem:

- The patient population included in the trial matches that of the final scope, i.e. adult patients with RRMM, previously treated with ≥2 lines of anti-myeloma therapy, including lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) given alone or in combination
- IsaPd is directly compared with Pd alone in ICARIA-MM. An indirect comparison with PanVd has been performed (in Appendix K)
- The key outcomes, as outlined in the NICE scope, have been evaluated in ICARIA-MM, i.e. PFS, OS, response rates, AEs and HRQoL
- It is expected that isatuximab meets EOL criteria based on precedent by NICE for other treatments reimbursed in the 4L setting and the evidence from the ICARIA-MM trial (Table 32).

B.2.14.3 *The uncertainty in the ICER estimates can be reduced by further data collection*

The results presented in this submission should be viewed in light of the level of censorship on the PFS and OS outcomes, the latter of which is a key driver of the model results. In patients who received 3 prior lines of treatments, at study cut-off, 43.1% of patient on Pd and 55.8% on IsaPd were censored in terms of PFS, meaning that 56.9%

of patients on Pd had progressed and 44.2% on IsaPd had progressed and therefore inform the parametric extrapolations. In term of overall survival, 41 (78.8%) and 35 (60.3%) patients in the IsaPd and Pd arms, respectively, were still alive and were, consequently, censored. This means that, for the analysis of OS in the 4L population, data were available for only 21−40% of patients on which to base the parametric extrapolations for the lifetime of the model.

Therefore, the censoring in the ICARIA-MM trial leads to uncertainty in the OS extrapolation and a wide range of ICER estimates which will be resolved as more data become available. The table below list key evidence sources initiated by the Sanofi. It also highlights evidence which can be collected via CDF to reduce uncertainty and understand outcome in a UK setting.

Evidence	Expected Date	Information available
ICARIA Final overall survival	[redacted]	The final analysis of survival will take place after at least 220 deaths have been observed.
UK Chart review	**Q1, 2021**	A real-world evidence study designed to evaluate treatment patterns, sequelae, and survival outcomes in patients with RRMM. This chart review will include 100 patients from the UK
EAMs	**Q4, 2019 – Q4, 2020**	As a PIM dug, isatuximab becomes a candidate for Early Access to Medicines Scheme (EAMS). Pending positive EAMS scientific opinion this is expected start in December 2019 and continue until marketing authorisation. EAMS can provide information on UK patient characteristics.
HES study	**2020**	Aim is to map pathway and resource use for patients 2nd line and later.
SACT data collection prior to CDF	**Q4, 2019 – Q4, 2020**	Sanofi is exploring the opportunity to include EAMS patients within the SACT dataset prior to MA.
CDF	**Post NICE TAG, duration ~2-3 years**	Given the immaturity in the ICARIA data set leading to significant uncertainty in the ICERs along with unbalanced use of daratumumab post progression between the IsaPd and Pd arms we strongly believe that IsaPd is a candidate for the CDF. Routing into the CDF is expected to resolve much of the uncertainty in the current evidence base for UK patients.

B.2.14.4 *IsaPd meets EOL criteria despite the availability of treatment options at 4L*

The table below outlines the data available to support IsaPd meeting the NICE EOL criteria in the 4L setting. Despite available treatment options at 4L, there remains a high unmet clinical need for treatments that extend progression-free time.

Table 32: 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	Median OS in patients with MM who have received two or more lines of therapy is 7.9 months to 15.2 months. In heavily pre-treated patients who received 3 prior lines of treatment, including lenalidomide, the life expectancy without IsaPd would be less than 24 months. In 2017 during the appraisal of pomalidomide (TA427) (4), NICE Appraisal Committee stated that in patients who received 3 or more prior therapies, the criterion for short life expectancy was met compared to standard of treatment at the time. In March 2018, the appraisal committee reviewing a daratumumab monotherapy said that "life expectancy for people with relapsed and refractory multiple myeloma and was satisfied that it was less than 24 months" (TA510) (3). Both these treatments which are part of current standard of care at 4L, have reported median overall survival of less than 2 years (TA410, TA510) (3, 78) In the ICARIA-MM trial, the median OS for 4L patients on Pd was 14.36 months and median PFS was 7.82 months	Section B.1.3.2, page 19 Section B.1.3.7, page 22
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	Overall survival data are not yet mature. However, in the ITT population, at approximately 1 year of follow-up, a trend toward longer OS for IsaPd vs Pd alone, with an early separation of the survival curves (Figure 15), was observed (HR=0.687; [95% CI; 0.461, 1.023]). At the time of the analysis, the probability of surviving (95% CI) 12 months was 0.720 (95% C; 0.636, 0.787) in the IsaPd arm and 0.633 (95% CI; 0.545, 0.709) in the Pd arm. Progression-free survival for 4L patients treated with IsaPd was 13.3 months. Overall survival data are not yet mature. According to the KM curve, the survival probability at 3 months on IsaPd is 98%. Based on the parametric extrapolations used in the model, the median predicted OS is 2.8 years	Section B.2.6.1.1 Page 49 Section B.2.6.1.2, Page 54

Abbreviations: CI, confidence interval; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; KM, Kaplan-Meier; MM, multiple myeloma; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; Pd, pomalidomide, low-dose dexamethasone; PFS, progression free survival.

B.3. Cost effectiveness

Summary

- A four-state partitioned survival model (PSM) has been developed to evaluate the cost-effectiveness of IsaPd in RRMM from the perspective of the UK NHS. A life-time time horizon is applied, and costs and benefits are discounted at 3.5% per annum
- The base case compared IsaPd with Pd in patients who have received three prior lines of therapy including lenolidomide and a proteasome inhibitor. In UK clinical practice this equates to a 4L setting
- The population reflects the most likely positioning for IsaPd in the UK clinical pathway based on the IsaPd label (post lenolidomide), position of pomalidomide (the comparator in ICARIA-MM) in the treatment pathway and UK clinical expert advice
    - Estimates of PFS, duration of treatment, and OS for IsaPd and Pd were based on data from the ICARIA-MM trial. The model includes costs for medications, medication administration, follow-up, monitoring, terminal care costs, and costs of treatment of adverse events, which were based on published sources. Utility values for the different health states in the model were based on data from ICARIA-MM
    - We have assumed a confidential patient access scheme (PAS) is in place for pomalidomide and this was tested in the sensitivity analysis.
    - In the 4L setting patient outcomes are poor with current options: PFS <6 months and OS <2 years. IsaPd has a potential to substantially improve survival outcomes compared with currently available treatments. However, the ICER of IsaPd compared with Pd (a standard treatment in 4L) exceeds the EOL willingness-to-pay (WTP) threshold of £50,000/QALY. This is not surprising given the combination of two branded treatments, one of which, pomalidomide has been recommended by NICE under the EOL threshold and with an ICER already at the margin of the threshold. The addition of a second drug would automatically result in an ICER that is higher than the EOL threshold.
    - Despite the unprecedented clinical efficacy in terms of PFS and OS in a robust, placebo-controlled study, this case highlights the inherent challenges for combination oncology products. There is the risk of denying patients access to new treatments that offer more benefit compared with current treatments that have previously been accepted for use by NICE.
    - By submitting this case to NICE, Sanofi seek to engage with NICE, the CDF and NHSE to find solution to enable access to IsaPd for patients in the 4L setting

B.3.1 *Published cost-effectiveness studies*

A systematic literature review (SLR) was conducted to identify relevant economic evaluations of treatments for patients with RRMM. A detailed description of the review methods and full results and quality assessment of the identified studies are reported in

Appendix H. The review identified no eligible published cost-effectiveness studies for isatuximab in the treatment of RRMM.

Twenty studies were identified as eligible. The majority of studies were cost-utility analyses (n=18) and two studies were cost-effectiveness analyses without quality of life outcome data. All of the studies were models, and many of them used a semi-Markov or partitioned survival model structure.

The four NICE appraisals identified in the review were deemed relevant for further review and helped to inform this economic analysis: pomalidomide (TA427) (4), daratumumab monotherapy (TA510) (3), panobinostat (TA380) (39) and ixazomib (TA505) (61). These appraisals were reviewed to understand the methods and the data used in economic evaluations in RRMM presented to NICE and these were used to inform the approach taken for this appraisal. The most recent and relevant appraisals, pomalidomide (TA427) (4), and daratumumab monotherapy (TA510) (3) have been used to inform some model inputs, as both pomalidomide and daratumumab monotherapy have been recommended by NICE are treatment options for 4L. Daratumumab monotherapy is only recommended for use in England/Wales via the CDF.

B.3.2 *Economic analysis*

The base case evaluates the cost-effectiveness of IsaPd vs Pd and is informed primarily by the ICARIA-MM trial. A secondary cost-effectiveness analysis has also been performed for IsaPd compared with PanVd to satisfy the requirements of the NICE scope. This analysis, exploratory in nature, is informed by a match-adjusted indirect comparison and reported in Appendix K.4. From here on, only information relevant to the comparison between IsaPd and Pd is reported.

B.3.2.1 *Patient population*

The population in the base case is derived from a subgroup from the ICARIA-MM trial, i.e. patients who received three prior lines of therapy, including lenolidomide and a PI. In England and Wales, it is anticipated that IsaPd will be used in patients who have received three prior lines of treatment (i.e. 4L), including lenalidomide, for the following reasons:

- To be eligible for IsaPd treatment, patients must have already received lenalidomide and PI treatment. In England and Wales, lenalidomide (in combination with low dose dexamethasone) is recommended by NICE at 3rd line (3L) and, according to market research, is generally used at 3L (46)

- Pd (the comparator in ICARIA-MM) is recommended by NICE and used in patients who are at their third or subsequent relapse (4L+) and have received lenalidomide and bortezomib previously (4)

- Clinical expert opinion sought during Sanofi Advisory Board supports a 4L position based on unmet need (79)

A summary of the baseline characteristics used in the model is shown in Table 33. All baseline characteristics are based on information derived from patients on IsaPd or Pd in the 4L population of ICARIA-MM. Although the patients entering the model are younger

than those expected to be treated in the UK, evidence from ICARIA demonstrates consistent outcomes across all pre-specified subgroups including age (<75 years versus >=75 years) and number of previous lines (2 or 3 versus >3). (See Section B.2.6).

Table 33: Baseline characteristics used in the economic model

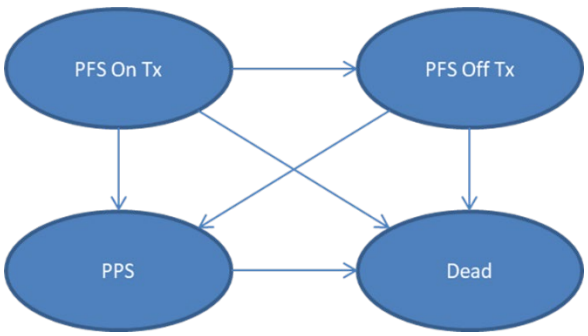
Variable	Model input
Age, years	65.9
Percentage male, %	51.8
Weight, kg	73.3
Body surface area, m^2	1.8

Additional analyses were also conducted for the ICARIA-MM ITT population and two post-hoc analyses of patients who had received two prior lines (3L) and for patients who had received three or more prior lines (4L+). These analyses were conducted specifically to address the NICE scope and are reported in Appendix K.3 as supplementary analyses. The remainder of this section describes the base case analysis for the anticipated place in UK clinical practice at 4L.

B.3.2.2 *Model structure*

A PSM was developed to estimate expected PFS, OS, lifetime costs of treatment and QALYs in patients in the eligible population who are assumed to receive treatment with IsaPd or Pd. A simplified schematic of the model is shown in Figure 20.

Figure 20: Simple schematic of partitioned survival model structure



Abbreviations: PFS, progression free survival; PPS, post-progression survival; Tx, treatment.

A four-state model was used in this instance to allow for the possibility that patients might stop therapy prior to disease progression and for utility values to differ for patients who are progression free and on treatment vs progression free and off treatment.

To account for the fact that some patients may continue treatment after progression (as seen in ICARIA-MM), the model also includes “one-off” incremental QALYs assigned at the point of progression to reflect any incremental effects of treatment post-progression. These incremental effects on QALYs are calculated by multiplying the average duration of treatment post progression with the difference in utility for patients who are on-treatment vs off-treatment. A similar model structure was previously accepted by NICE in the Pd appraisal (TA427) (40).

The model states were defined on the basis of progression-free survival (PFS), time to discontinuation (TTD), and overall survival (OS), which were derived directly from the ICARIA-MM trial. The model includes costs for medications, medication administration and dispensing costs, follow-up, monitoring, terminal care costs, and costs of treatment of adverse events which were based on published sources. Utility values for the different health states in the model were also based on data from ICARIA-MM.

It should be noted that costs of medications and administration are calculated based on distributions for TTD independently of PFS, PFS on treatment, and OS. According to the ICARIA-MM trial protocol, patients were treated until progression. Progression was assessed by blood tests; An average of 2 months after a blood sample was collected was needed to determine progression. This means that the majority of patients remained on treatment after progression. Therefore, the post-progression (on-treatment) state is designed to capture the 76.8% of IsaPd patients who received the study drug (IsaPd) for 2.02 months after progression, and the 73.8% of Pd patients who received study drug (Pd) for 1.66 months after progression in the ICARIA-MM trial. According to UK clinical experts, this is not uncommon in clinical practice where patients may continue treatment following progression (due to the need for a confirmatory test for progression, scheduling of clinic appointments, etc.) (79). Hence to reflect expected clinical practice the model estimates cost of treatment based on TTD and not PFS and constrains the TTD distribution to never exceed the PFS distribution to prevent overestimation of benefits and underestimation of costs. Post-progression (off treatment) reflects those patients who progressed and received post study/subsequent therapies in ICARIA-MM.

B.3.2.2.1 Rationale for model structure

In the SLR of prior economic evaluations of treatments for RRMM described above (Section B.2.1), it was seen that PSMs have been used extensively in economic evaluations in this setting. The main advantage of the PSM approach vs the Markov approach is that it provides a much closer fit to the actual PFS and OS data (that is, Kaplan-Meier [KM] curves) as observed in the clinical trials. It allows the time dependency in the risk of events over time to be captured due to survival being modelled as a function of time since model entry. Although the KM curves for IsaPd are immature, using an approach that aligns with the available data is important given that existing CD38 treatment is associated with long-term survival patterns (41). Isatuximab, also a CD38 agent, is expected to demonstrate similar long-term survival patterns; as a result, the structure needs to be sufficiently flexible to align closely with the available data and allow for exploration of these patterns.

PSM models were used in the manufacturers' submissions to NICE for TA510 of daratumumab monotherapy (3, 41) and TA338/TA427of pomalidomide with dexamethasone (4, 40). For the former, the rationale for using the PSM was that this approach had been used in previously accepted economic models in RRMM and "that it would capture the key clinical outcomes of time to treatment discontinuation, PFS and OS" (41).

In their review of published completed HTAs of cancer treatments, the NICE DSU reported that PSM was used in 22 of 30 assessments (80). The DSU did not provide explicit guidance on when to use PSM vs a Markov cohort model (MCM), but specified

that when using PSM, the modeling method be clearly stated, the model choice be rationalised on the bases of theoretical and practical considerations, the main structural assumptions be reported, and the specific limitations on extrapolation be highlighted. While this document therefore does not provide proscriptive guidance on use of PSM vs other modeling approaches, it suggests that PSM is a reasonable approach if a rationale for its use is provided as we have done above.

Taken as a whole, we therefore believe that a PSM is appropriate as it has been used in numerous prior HTA assessments including assessments of treatments for RRMM in a similar setting. The economic modelling approach was validated by clinical and health economic experts during model development. Details of the validation process undertaken are presented in Section B.3.3.3.

B.3.2.2.2 Perspective

For this evaluation, a UK NHS/PPS perspective is employed, consistent with the NICE reference case. Only direct medical care costs related to the treatment of RRMM were therefore considered.

B.3.2.2.3 Time horizon

All outcomes were evaluated over a 15-year time horizon, beginning with the start of treatment. The economic models included in manufacturers' submissions to NICE for Dara monotherapy and Pd used 15-year time horizons (41). In the model included in the manufacturer's submissions for PanVd, a time horizon of 25 years was used (81). We have chosen to use a 15-year time horizon for this submission, corresponding to that used for Dara monotherapy and Pd. Clinicians we have spoken to agreed that this will be sufficient to approximate a lifetime projection in the populations of interest and we note that has been previously accepted by NICE at this point in the treatment algorithm.

B.3.2.2.4 Cycle length

The model has a periodicity (e.g., model cycle length) of one week, which permits accurate representation of the dosing regimens for IsaPd and potential comparators (which have dosing regimens of once every 2, 3, or 4 weeks). Given a 15-year time horizon and a weekly cycle duration, the model estimates outcomes and costs over a total of 15 years x 52.18 weeks/year = 783 cycles. Given the relatively short cycle length, a half-cycle correction has not been applied.

B.3.2.2.5 Discounting

LYs, QALYs, and costs are reported on an annual discounted and undiscounted basis, beginning with the second year of the modeling time horizon. The model assumes an annual discount rate of 3.5% for the UK setting in the base case. In a scenario analysis, a discount rate of 1.5% for health effects and costs were tested.

Table 34: Features of the economic analysis based on relevant comparators identified in NICE scope

	Previous appraisals				Current appraisal	
Factor	**TA427 (pomalidomide)**	**TA380 (panobinostat)**	**TA505 (Ixazomib)**	**TA510 (dara monotherapy)**	**Chosen values**	**Justification**
Model type	CUA	CUA	CUA	CUA	CUA	NICE reference case (82)
Time horizon	15 years (lifetime)	25 years (lifetime)	25 years (lifetime)	15 years (lifetime)	15 years (lifetime)	NICE reference case (82) recommends life-time horizon
Model Cycle length	1 week	3 weeks	1 week	1 week	1 week	Accounts for dosing schedules for different treatments being compared
Half-cycle correction	No	Yes	No	No	No	Short cycle length, no need for correction
Source of utilities	Utility data came from the MM-003 trial (EQ-5D estimates).	Trial based EORTC-30 mapped to EQ-5D	Utility scores were mainly taken from the TMM1 trial.	Utility scores were mainly taken from the MM-003 trial.	Utility data sourced from ICARIA study	NICE reference case (82)
Source for resource use	Resource use data came from clinical trials and UK patterns	Resource use data came from clinical trials and UK patterns	Resource use were taken from patient-level data of the TMM1 trial and from several other published studies.	Resource use was taken TA338), from experts' opinion and from the pivotal RCTs.	Resource use were informed by daratumumab submission (TA510) and validated with UK expert opinion	The resource use based on UK expert opinion (1)
Source for costs	In general, costs were from conventional sources relevant to the NHS (e.g. MIMs, NHS reference costs, BNF) as well as other oncology submissions				NHS reference costs, BNF and eMIT	NICE reference case (82)

Source: Isatuximab final scope (83)

B.3.2.2.6 Intervention technology: Isatuximab (in combination with pomalidomide and dexamethasone)

The intervention of interest is IsaPd. This treatment corresponds to the treatment arm of the ICARIA-MM trial. Isatuximab is administered as an intravenous infusion (IV) in combination with pomalidomide and dexamethasone, according to the schedule:

- Isatuximab 10 mg/kg IV was administered on Days 1, 8, 15, and 22 at Cycle 1, and then on Days 1 and 15 for subsequent cycles
- Dexamethasone 40 mg (or 20 mg if the patient was ≥75 years old) PO (the preferred route) or IV (if PO route could not be used) was administered on Days 1, 8, 15 and 22
- Pomalidomide 4 mg PO was taken on Days 1 to 21 of each 28-day cycle

B.3.2.2.7 Isatuximab Premedication

Premedication should be used prior to isatuximab infusion with the following medications to reduce the risk and severity of infusion reactions (IRs):

- Dexamethasone 40 mg PO or IV (or 20 mg PO or IV for patients ≥75 years of age).
- Acetaminophen 650 mg to 1000 mg PO (or equivalent).
- H2 antagonists (ranitidine 50 mg IV or equivalent [e.g., cimetidine]), or oral proton pump inhibitors (e.g., omeprazole, esomeprazole).
- Diphenhydramine 25 mg to 50 mg IV or PO (or equivalent [e.g., cetirizine, promethazine, dexchlorpheniramine]). The intravenous route is preferred for at least the first 4 infusions.

The above recommended dose of dexamethasone corresponds to the total dose to be administered only once before the infusion, as part of the premedication and the backbone treatment, before isatuximab and pomalidomide administration.

B.3.2.3 *Comparator: Pomalidomide (in combination with dexamethasone) (Pd)*

The relevant comparator is pomalidomide in combination with dexamethasone and is administered according to the following schedule.

- Dexamethasone 40 mg (or 20 mg if the patient is ≥75 years old) PO or IV given on Days 1, 8, 15 and 22
- Pomalidomide 4 mg PO given on Days 1 to 21 in a 28-day cycle

The comparator in the model base case is consistent with the NICE scope for the evaluation of Isa in RRMM and the treatment most likely to be displaced by the introduction of IsaPd. Further exploratory analyses are provided for PanVd in Appendix K4 to meet the requirements of the scope.

B.3.3 *Clinical parameters and variables*

Since a lifetime time horizon is required for the area under the curve (AUC) partitioned survival approach and current data for IsaPd are not mature, it was necessary to extrapolate the available data until all patients have progressed or died.

Estimates of PFS, TTD, PFS on treatment, and OS for IsaPd and Pd were derived by fitting parametric survival distributions, accordance with the NICE DSU Technical Support Document (TSD) (84, 85), to the individual patient failure time data for patients who received 3 prior line of treatment from ICARIA-MM. (4L patients).

Plots of Schoenfeld residuals were generated to assess the proportional hazards (PH) assumption. Diagnostic plots for treatment effects were generated as plots of the negative log and the log-negative-log of survival probabilities against time (months) and the log of time. Additionally, diagnostic plots for the nature of treatment effects were produced using an extension of an approach proposed by Bagust and Beale and in accordance with recommendations from the NICE DSU TSD on survival analysis (84, 85). With this extended approach, an estimated treatment effect for each of four different treatment effect assumptions (i.e., constant shift in survival time, accelerated failure time, PH, and proportional odds) were applied to failure times in the control group to obtain a counterfactual KM survival distribution for the control group reflecting the expected outcome had those patients received study treatment with the specified treatment effect assumption. The counterfactual control group survival distributions were then compared with the observed survival distributions for the group receiving study treatment. If the treatment effect assumption is accurate, the two curves should overlap. Restricted mean survival time (RMST) was also calculated and plotted for each treatment based on the KM distribution and the parametric survival distributions.

For each of the outcomes used in the model, five standard distributions were estimated (exponential, Weibull, log-logistic, lognormal, generalised gamma). Generalised F and Restricted cubic spline (RCS) distributions were also estimated. Flexsurv, an R package for fully-parametric modelling of survival data (86) was used to consider a wide range of parametric distributions in order to select the most appropriate for the base case. The distributions used in the base case model were selected based on fit statistics, visual inspection of survival distributions, hazard functions, time dependent HRs, and diagnostic plots for treatment effects, as well as clinical plausibility. The Bayesian Information Criterion (BIC) was used as the primary measure of statistical fit, as this statistic places a relatively high penalty on the number of parameters included in the distribution and hence avoids placing undue influence on the tail of the distribution which can have a large effect on long-term survival projections. The distributions which resulted in extremes (highest and lowest) in estimates were tested in the sensitivity analysis (SA).

The same survival distribution for the two treatment arms of ICARIA-MM was used. The rationale for assuming the same distribution is that it facilitates the comparison of fit statistics across distributions and parameterisation of the treatment effect and avoids consideration of an unwieldy number of potential combinations of distributions. Also, given the large number of distributions considered, including distributions with many parameters (e.g., the generalised F distribution has four parameters, the RCS

distributions have six parameters, not including the knots) means that it is generally feasible to identify adequate distributions without relaxing this assumption.

Full details of the methodology, KM survival distributions, hazard rates, HRs, Schoenfeld residuals, transformation diagnostics, and treatment effect diagnostics for each clinical outcome by treatment group for 4L patients in the ICARIA-MM trial are presented in Appendix K. RMSTs are also provided in Appendix K.

The remainder of Section B.3.3 describes results of parametric survival analyses to capture and extrapolate OS, PFS and TTD data from ICARIA-MM over a lifetime horizon.

B.3.3.1 *Incorporating the clinical data for IsaPd and Pd into the model*

B.3.3.1.1 Overall survival

Following the NICE DSU methodology discussed above, the exponential distribution was used for OS for IsaPd and Pd in the base-case analysis. This was based on the treatment effect diagnostics and test of linearity of Schoenfeld residuals for the PH assumption, statistical goodness of fit (lowest BIC), acceptable visual fit and projections of OS that were clinically plausible and consistent with long-term OS data from pivotal trial for Pd (MM-003) (Table 35). Best- and worst-case distributions were tested in the SA.

Table 35: Parametric distribution used for OS

Distribution	Exponential
BIC rank	First
Visual inspection	Acceptable, though possibly underestimates OS for IsaPd at the tail of the distribution
Treatment effect	PH treatment effect consistent with treatment effect diagnostics and test of linearity of Schoenfeld residuals
Clinical plausibility	Projections of OS for Pd consistent with long-term OS data for Pd arm of MM-003 given better prognosis of patients in 4L subgroup of ICARIA-MM compared with MM-003 demonstrated by comparison of observed PFS and OS curves for Pd arms of two studies
Comment	Projected RMST at 15 years for Pd, IsaPd, and the difference between IsaPd and Pd were in the middle of the range of estimates generated by all the distributions considered

Abbreviations: BIC, Bayesian Information Criterion; OS, overall survival; PFS, progression-free survival; PH, proportional hazard; RMST, restricted mean survival time.

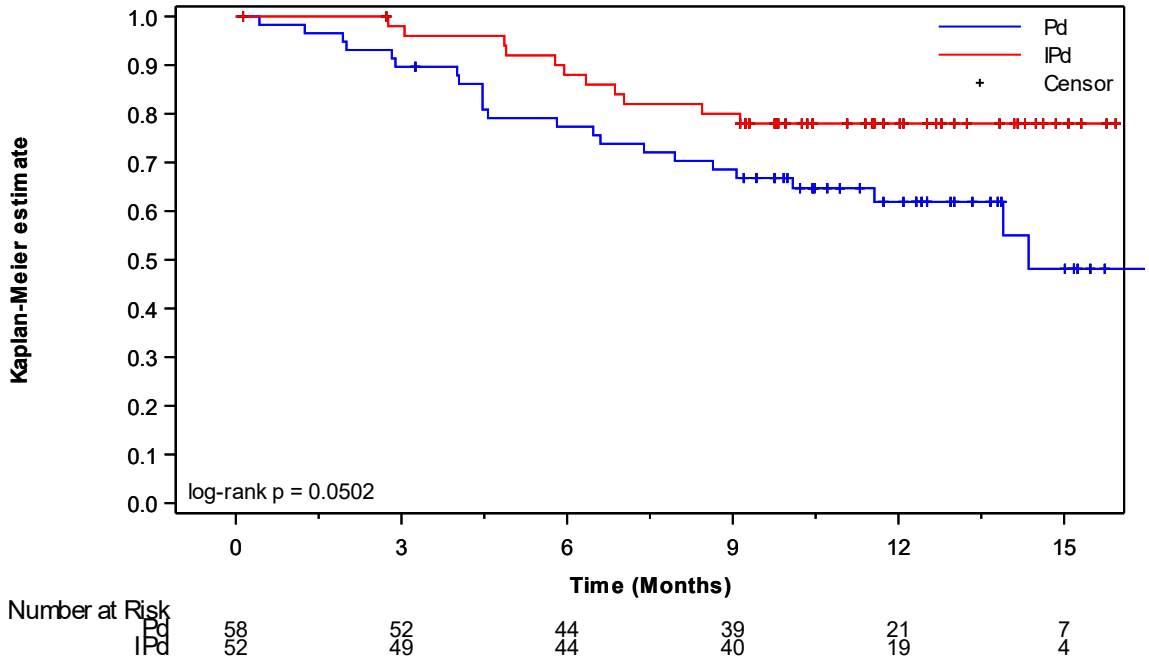
Rationale for curve selection

- **KM curve for overall survival from ICARIA-MM**

At the time of the study cut-off date (median follow-up time was 11.56 months in the IsaPd arm and 11.73 months in the Pd arm of the ICARIA-MM trial), the median OS had not been reached. At this time, 34 patients out of 110 (31%) had died (11 in IsaPd arm and 23 in Pd arm), resulting in 60.3% censored on Pd arm and 78.8% on the IsaPd arm. Due to the incomplete data, parametric model extrapolation was used to capture OS

over a lifetime horizon (Figure 21), was based on 39.7% deaths on Pd arm and 21.2% deaths on IsaPd arm

Figure 21: OS in the ICARIA-MM Trial (4L)



Abbreviations: IPd, isatuximab, pomalidomide, low dose dexamethasone; OS, overall survival; Pd, pomalidomide, low dose dexamethasone

- **Diagnostic and proportional hazard assumption tests**

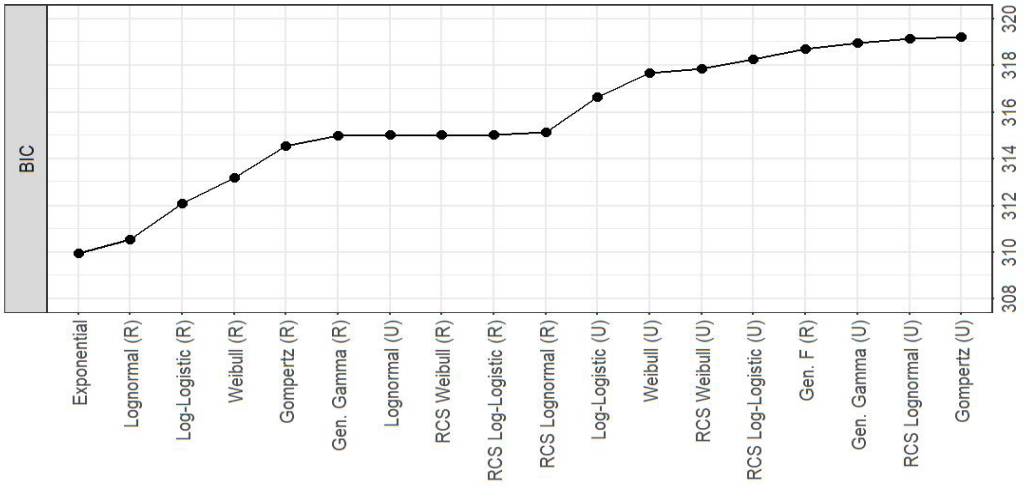
The test of the linearity of the Schoenfeld residuals is not statistically significant, suggesting that a PH distribution (e.g., exponential, Weibull, Gompertz) is not inappropriate. The cumulative hazard function (log of survival by time) has a slightly decreasing slope for both arms, especially IsaPd (with the exception of the tail of the distribution Pd where the numbers at risk are small), suggesting that distributions with diminishing hazards may also not be inappropriate. The treatment effect diagnostics indicate that PH, proportional odds, and accelerated failure time (AFT) models may all be appropriate. Thus, although the KM curve and cumulative hazard function for IsaPd suggest diminishing risk and possibly increasing benefit for IsaPd vs Pd after 9 months, the other diagnostics do not generally support this conclusion.

KM survival distributions, hazard rates, HRs, and Schoenfeld residuals, transformation diagnostics, and treatment effect diagnostics for OS by treatment group for 4L patients in the ICARIA-MM trial are reported in Appendix K.

- **Goodness of fit**

Goodness of fit was assessed by visual assessment of model curves versus KM data, shown in Figure 21, and using Bayesian Information Criterion (BIC) statistics. A ranking of parametric distributions fit to OS by the fit statistics are shown in Figure 22.

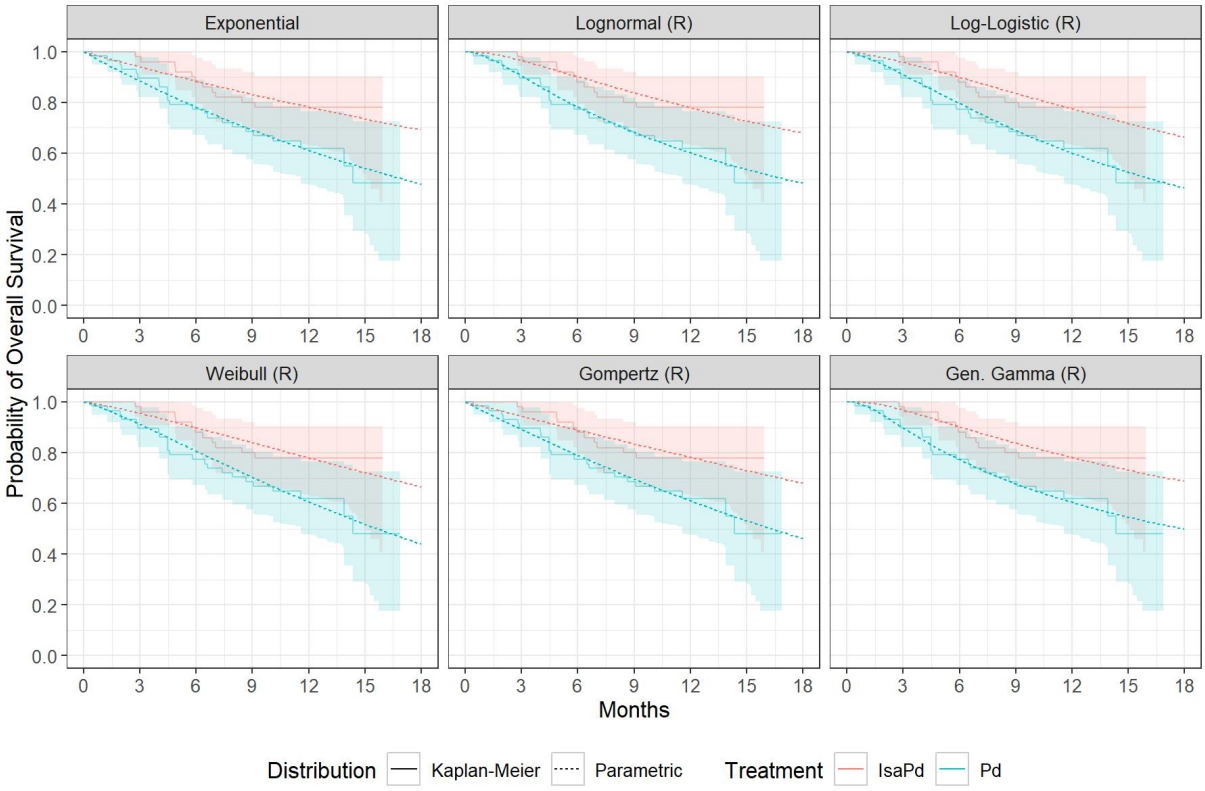
Figure 22: Fit statistics for parametric distributions fit to OS for the 4L population of ICARIA-MM



Abbreviations: BIC: Bayesian Information Criterion (smaller is better); OS, overall survival; R, restricted; RCS, restricted cubic spline; U, unrestricted.

Parametric survival distributions for OS during the trial period for the six best fitting distributions based on BIC are shown in Figure 23 (distributions are ranked by BIC going left to right, top to bottom). The top six best fitting distributions have similar visual fit to the KM curve through to the end of trial follow-up. While they all tend to have good visual fit to the KM curves for the Pd arm, they all tend to fit relatively poorly to the IsaPd arm, due to flat tail of the KM distribution for IsaPd beginning at approximately 9 months.

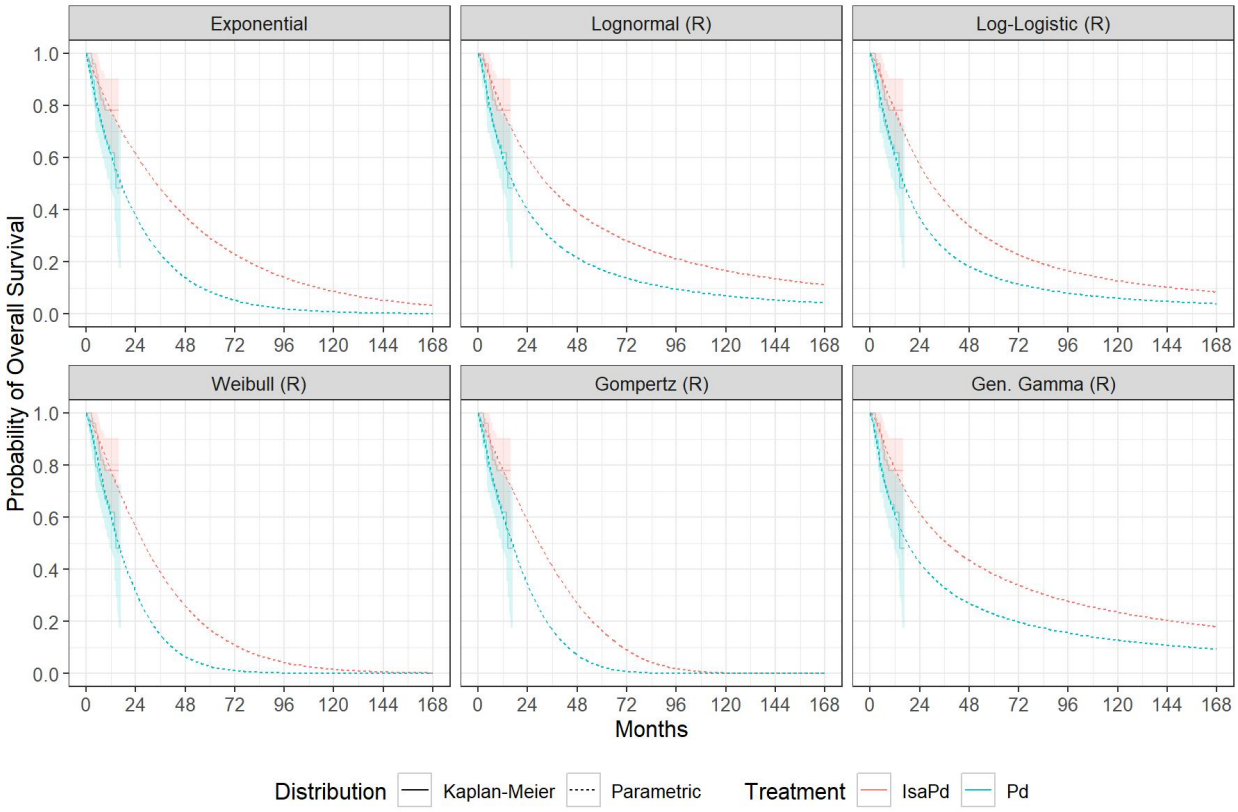
Figure 23: Parametric survival distributions fit to OS for the 4L population in ICARIA-MM, by randomised treatment



Abbreviation: OS, overall survival; R, restricted.

Long-term projections of OS (out to 15 years) for these six distributions are shown in Figure 24. The exponential distribution shows that virtually all patients projected to be dead by 8 years in the Pd arm and 14 years in the IsaPd arm. The restricted Weibull and restricted Gompertz have relatively lower separation and virtually all patients projected to be dead by 10 and 8 years on both arms, respectively. The restricted lognormal, restricted log-logistic and restricted generalised gamma all project approximately 10% or more of IsaPd patients remaining alive after 14 years.

Figure 24: Long-term projections of OS Based on parametric survival distributions fit to OS for the 4L population in ICARIA-MM, by randomised treatment



Abbreviation: OS, overall survival; R, restricted.

- **External/Clinical validation**

There are limited long-term data on OS in patients similar to those in the 4L subgroup of ICARIA-MM with which to assess the external validity of these projections. At 28 months, the maximum reported follow-up of the MM-003 trial, OS for Pd patients in the MM-003 trial was approximately 15%. In contrast, the restricted generalised gamma distribution projects OS of approximately 40% at 28 months, the exponential, restricted lognormal and restricted log-logistic distributions project OS of approximately 30% at 28 months, and the restricted Weibull and restricted Gompertz project OS of approximately 20% at 28 months.

Although the parametric distributions project OS for Pd at 28 months that is greater than that observed in the MM-003 trial, as noted above, the KM survival distribution for PFS for Pd patients in the MM-003 trial was below that for Pd patients in the 4L subgroup of ICARIA-MM, suggesting the former had poorer prognosis than the latter. A similar finding

is observed when comparing the OS for Pd patients in the two arms. Although the median OS for the Pd arm of the MM-0003 trial (13.1 months) was only slightly lower than that in the 4L subgroup of ICARIA-MM (approximately 14.3 months), the latter was heavily influenced by two deaths between 13 and 14 months at which point there were only approximately 10 patients remaining at risk resulting in a 20% decline in the PFS at that point. A comparison of the KM curves for OS for the Pd arm of MM-003 and the 4L subgroup of ICARIA-MM clearly suggest worse survival for Pd patients in the former than the latter. Given the better prognosis of Pd patients in the ICARIA-MM trial, the more favourable long-term projections based on the exponential distribution do not seem unreasonable.

Clinical validation was also sought from a group of three NHS consultant haematologists (B.3.3.3). Two experts selected Weibull as their preferred choice for OS and one expert selected exponential as his preferred choice. As seen in Figure 24, with Weibull, almost all patients are dead by 5 years on Pd arm and by 10 years on IsaPd. There are no patients alive after 10 years, which is inconsistent with the feedback and published evidence regarding long term survival for a small proportion of patients with RRMM (Section B.3.3.3). The exponential curve predicts around 10% alive at 10 years on isatuximab and all patients are dead by 15 years. On pomalidomide, almost all patients are dead by 10 years. This is discussed in Section B.3.3.3.

B.3.3.1.2 Progression-free survival

The restricted lognormal distribution was used in the base case based on visual and statistical goodness of fit (Table 36) Also, this distribution yields projections of the benefit of IsaPd for PFS that are approximately in the middle of the range of estimates from the various distributions considered. Although no external data are available to validate the long-term projections, this distribution yields projection of PFS for Pd that are below 15% at three years, below 5% at five years and close to zero by 10 years, which are not unreasonable given the relatively poor prognosis of these patients. Treatment effect diagnostics suggest that AFT models such as the lognormal are appropriate. The plot of the cumulative hazard function is suggestive of a diminishing hazard over time consistent with this distribution. (Appendix K1).

Table 36: Parametric distribution used for PFS for IsaPd and Pd

Chosen distribution	Lognormal (R)
BIC rank	First
Visual inspection	Good visual fit to the observed KM survival curves
Treatment effect	AFT model appropriate based on treatment effect diagnostics
Clinical plausibility	Although no external data are available to validate the long-term projections, distribution yields projection of PFS for Pd that are below 15% at three years, below 5% at five years and close to zero by 10 years, which are not unreasonable given the relatively poor prognosis of these patients.
Comment	Yields projection of benefit that is approximately in the middle of range of estimates from all distributions

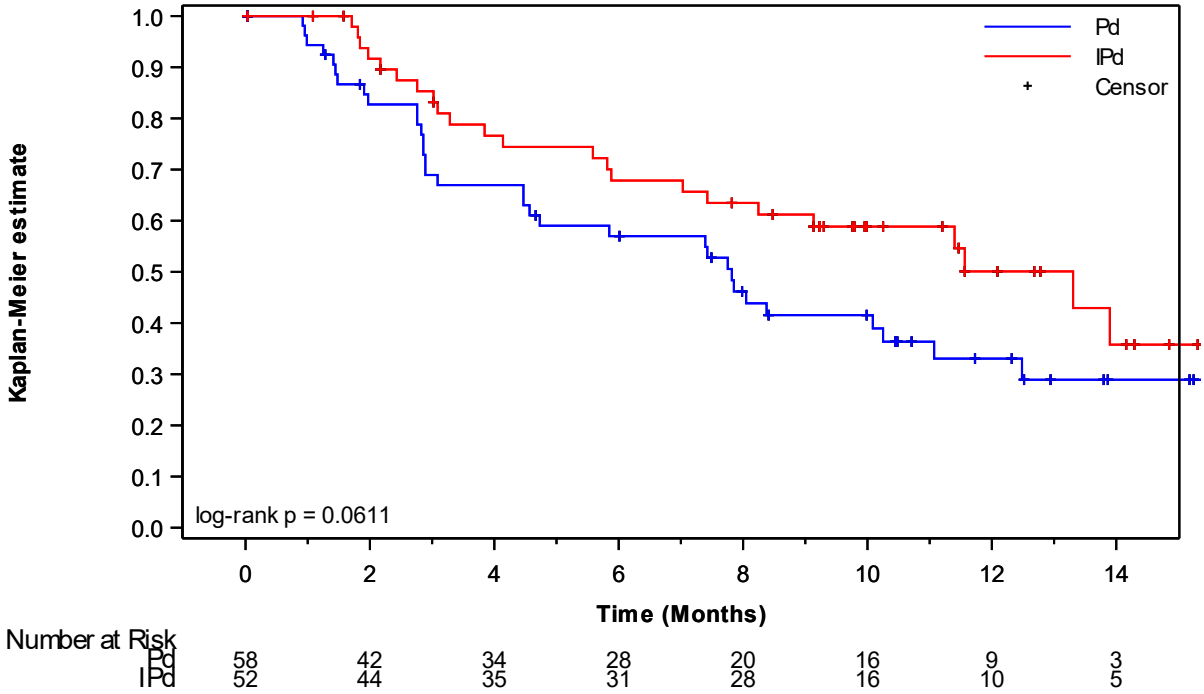
Abbreviations: AFT, accelerated failure time; BIC, Bayesian Information Criterion; IsaPd, isatuximab, pomalidomide, low dose dexamethasone; KM, Kaplan-Meier; Pd, pomalidomide, low dose dexamethasone; PFS, progression-free survival;

Rationale for curve selection

- **KM curve for PFS**

At the time of the cut-off date 43.1% of Pd and 55.8% of IsaPd patients were censored in terms of PFS, meaning that 56.9% on Pd and 44.2% on IsaPd had progressed and were used to inform the parametric extrapolation to estimate PFS over the life-time horizon (Figure 25).

Figure 25: PFS in the ICARIA-MM Trial (4L)



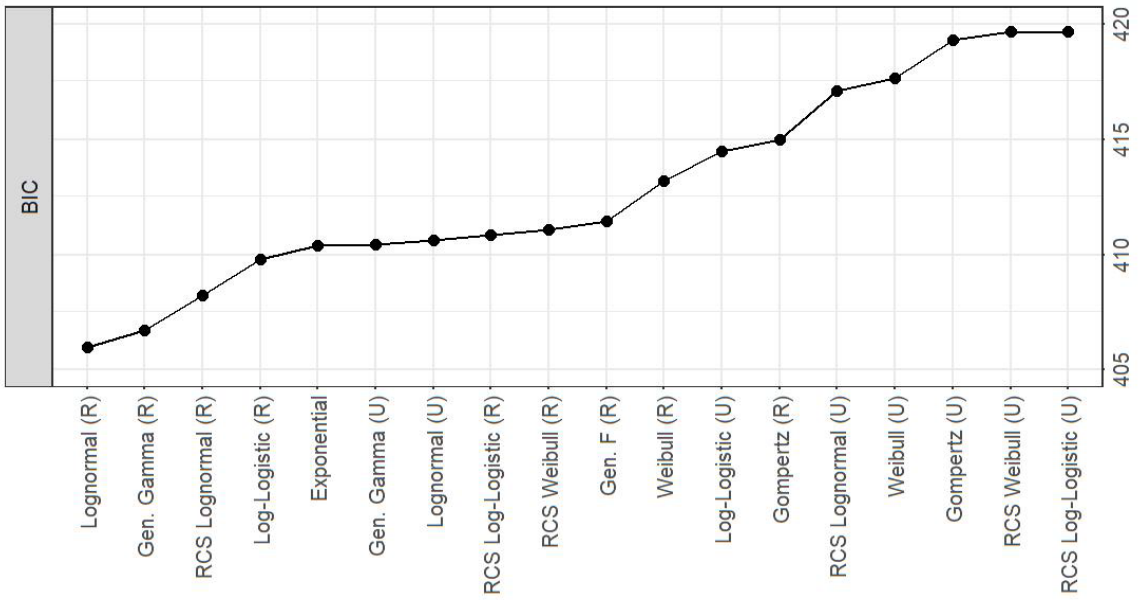
- **Diagnostic and proportional hazard assumption tests**

The test of the linearity of the Schoenfeld residuals is not statistically significant, suggesting that a PH distribution (e.g., exponential, Weibull, Gompertz) is not inappropriate. The cumulative hazard function (log of survival by time) has a slightly decreasing slope (with the exception of the tail of the distribution where the numbers at risk are small), suggesting that distributions with diminishing hazards may not be inappropriate. The treatment effect diagnostics indicate that PH, proportional odds, and AFT models may all be appropriate. KM survival distributions, hazard rates, HRs, and Schoenfeld residuals, transformation diagnostics, and treatment effect diagnostics for PFS by treatment group for 4L patients in the ICARIA-MM trial are reported in Appendix K.

- **Goodness of fit**

A ranking of parametric distributions fit to PFS by the fit statistics is shown in Figure 26.

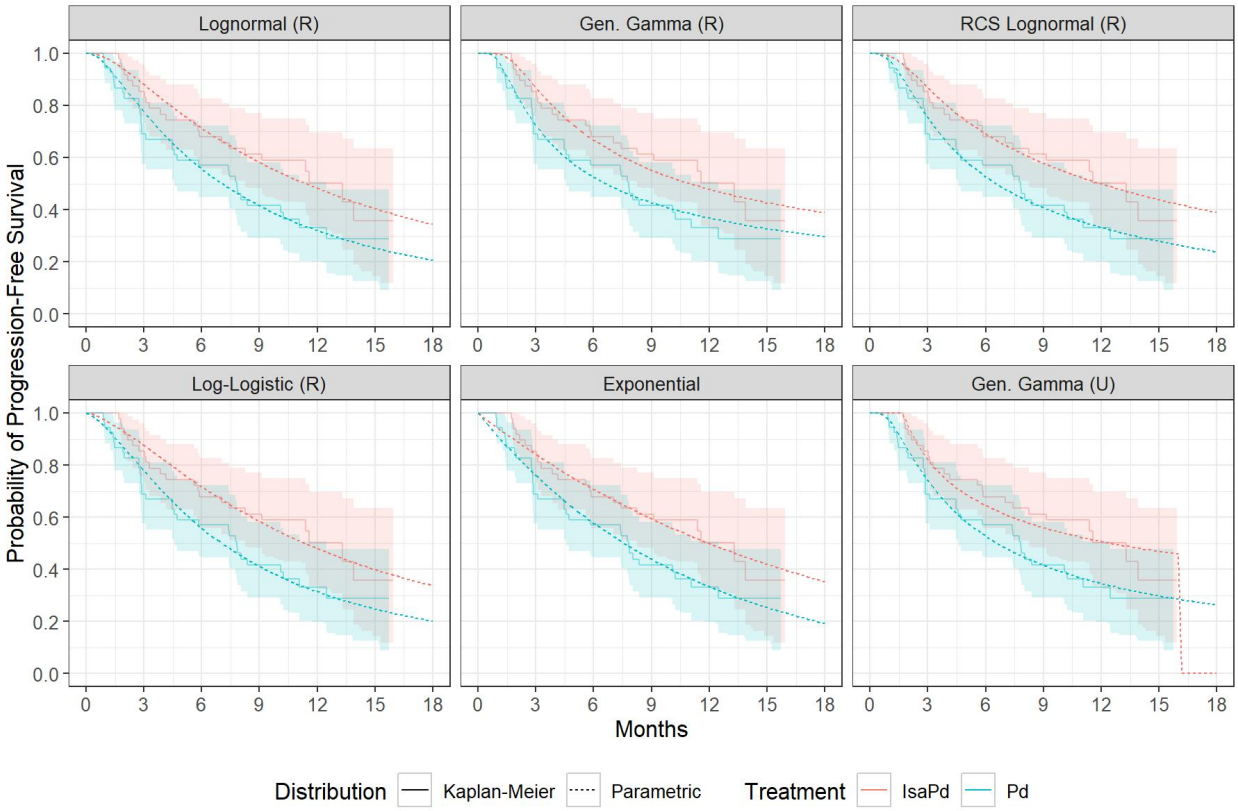
Figure 26: Fit statistics for parametric distributions fit to PFS for the 4L population of ICARIA-MM



Abbreviations: BIC; Bayesian information criterion (smaller is better); PFS, progression-free survival; R, restricted; RCS, restricted cubic spline; U, unrestricted.

Parametric survival distributions for PFS during the trial period for the six best fitting distributions based on BIC are shown in Figure 27 (distributions are ranked by BIC going left to right, top to bottom). All of the top fitting parametric distributions have relatively good fit to the KM distribution. The generalised Gamma distribution has a discontinuity at approximately 15 months, indicating that the solution for this distribution may not have converged. All the distributions generate projections of PFS probability at 18 months for Pd that range from approximately 20% to 30%, and for IsaPd range from 30% to 40%.

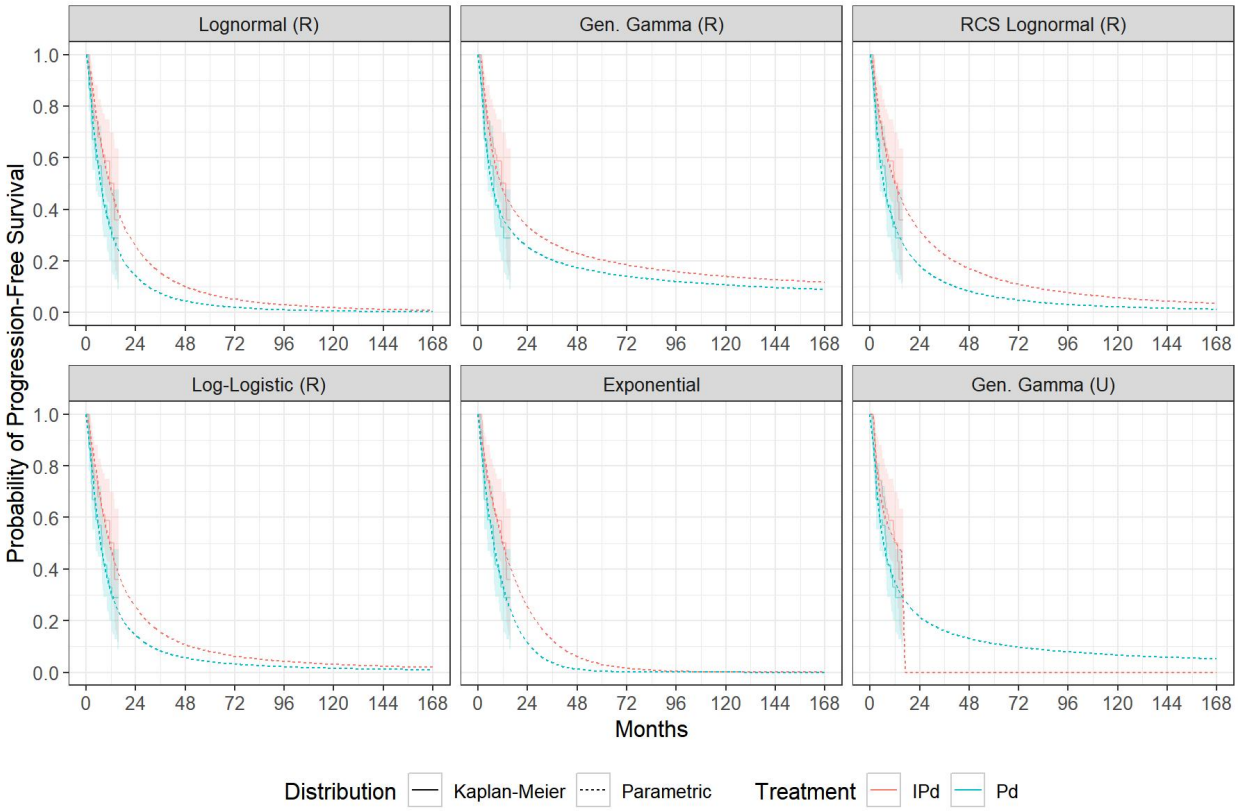
Figure 27: Parametric survival distributions fit to PFS for the 4L population in ICARIA-MM, by randomised treatment



Abbreviation: PFS, progression-free survival.

Long-term projections of PFS (out to 15 years) for these six distributions are shown in Figure 28. With the exception of the restricted and unrestricted generalised gamma distributions, PFS probability is projected to be less than approximately 5% for both IsaPd and Pd by 120 months and less than 10% for both IsaPd and Pd at 5 years. The PFS probability with restricted RCS lognormal distribution is approximately 12% at 5 years for IsaPd.

Figure 28: Long-term projections of PFS based on parametric survival distributions fit to PFS for the 4L population in ICARIA-MM, by randomised treatment



Abbreviation: PFS, progression-free survival.

➢ External/clinical validity of PFS

As with overall survival, there are no long-term data on PFS for patients similar to those in ICARIA-MM that can be used to assess the validity of long-term projections. Although data for PFS for Pd out to approximately 75 months are available from the MM-003 trial, median observed PFS for Pd in this trial (16 weeks = 3.7 months) was substantially less than that for patients receiving Pd in the subgroup of patients in ICARIA-MM receiving 4L treatment (approximately 7.5 months).

In the clinical validation exercise with NHS consultant haematologists, there was no consensus amongst the respondents on the preferred estimation for PFS, however there was a general agreement on the top three curves. The RCS Weibull (R), Weibull (R), and exponential curves appeared to be the preferred options, and one KOL also included Gompertz (R) in the top three. These were tested in sensitivity analysis (See section B.3.3.3)

B.3.3.1.3 Progression-free on treatment

The restricted lognormal distribution was used in the base case for PFS on treatment based statistical goodness of fit (lowest BIC), relatively good visual fit, AFT treatment effect consistent with treatment effect diagnostics, and predicted RMST for Pd, IsaPd, and the difference between IsaPd and Pd that are in the middle of the ranges of estimates from the various distributions considered (Table 37).

Table 37: Parametric distribution used for PFS on treatment for IsaPd and Pd

Distribution	Lognormal (R)
BIC rank	First
Visual inspection	Relatively good visual fit to the observed KM curves
Treatment effect	AFT treatment effect consistent with treatment effect diagnostics
Clinical plausibility	No external data are available to assess clinical plausibility of long-term projections
Comment	Predicted RMST for Pd, IsaPd, and the difference between IsaPd and Pd that are in the middle of the ranges of estimates from the various distributions considered

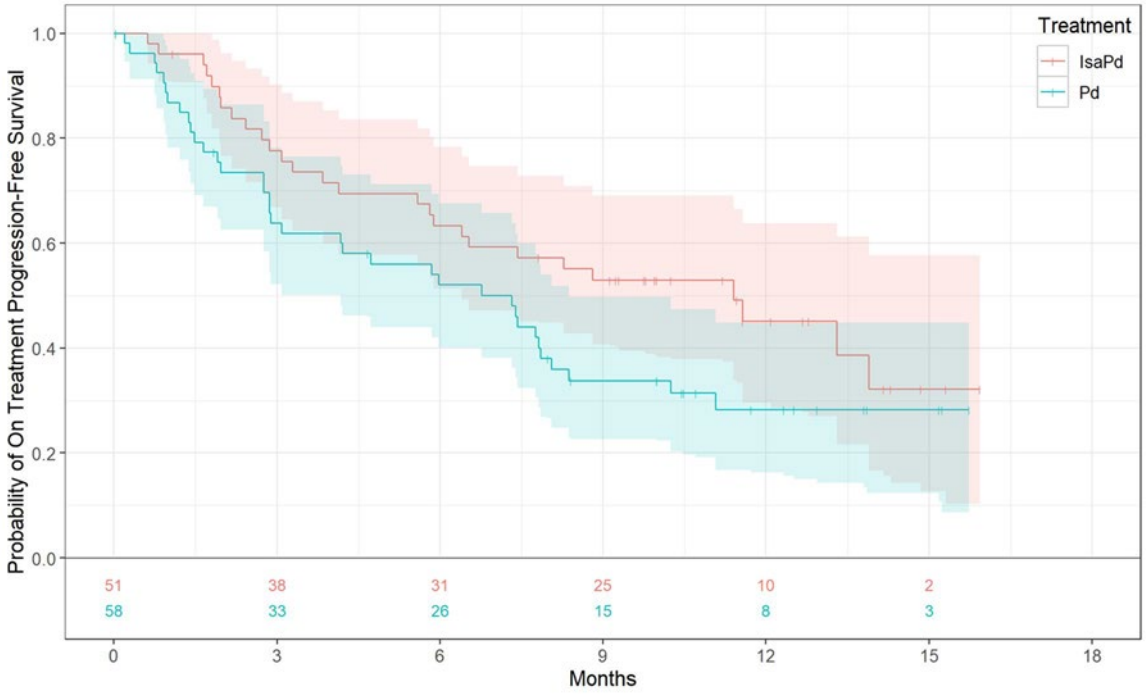
Abbreviations: AFT, accelerated failure time; BIC, Bayesian Information Criterion; IsaPd, isatuximab, pomalidomide, low dose dexamethasone; Pd, pomalidomide, low dose dexamethasone; PFS, progression-free survival; R, restricted.

Rationale for curve selection

- **KM curve for PFS-on treatment**

Figure 29 provides the KM curves for PFS-on treatment from ICARIA-MM. These data were used to inform the parametric extrapolation to estimate PFS on treatment over the life-time horizon.

Figure 29: KM curves for PFS-on treatment



Abbreviations: IsaPd, isatuximab, pomalidomide, low dose dexamethasone; KM, Kaplan Meier; Pd, pomalidomide, low dose dexamethasone; PFS, progression-free survival.

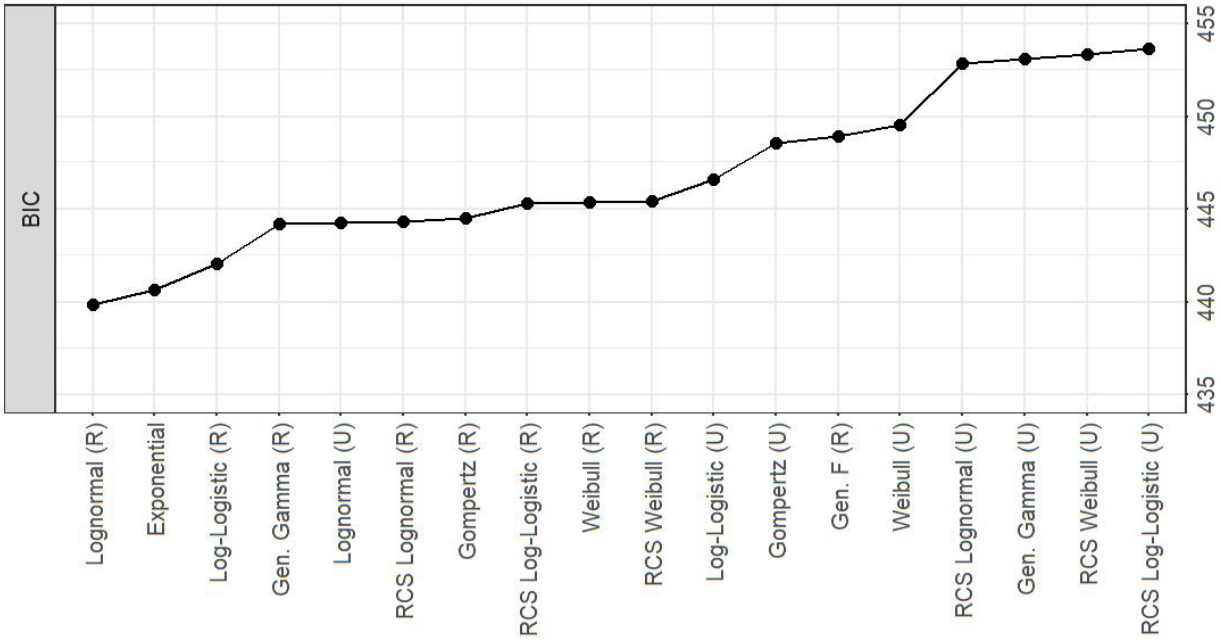
- **Diagnostic and proportional hazard assumption tests**

KM survival distributions, hazard rates, HRs, and Schoenfeld residuals, transformation diagnostics, and treatment effect diagnostics for PFS on treatment by treatment group for 4L patients in the ICARIA-MM trial reported in Appendix K. The hazard rates for the IsaPd and Pd groups overlap initially and become more stable after three months, where rates for IsaPd are lower than the hazards for Pd throughout the follow-up period. The HR for IsaPd vs Pd is fairly stable throughout the follow-up period. The p-value on the test of linearity of Schoenfeld residuals is not statistically significant suggesting that a PH distribution may not be inappropriate. The slope of the cumulative hazard function for IsaPd is somewhat diminishing (except for an increasing slope at the tail when relatively few patients remain at risk) suggesting a declining hazard over time. The treatment effect diagnostics suggest that an AFT model may be most appropriate.

- **Goodness of fit**

A ranking of parametric distributions fit to PFS on treatment by the fit statistics are shown in Figure 30.

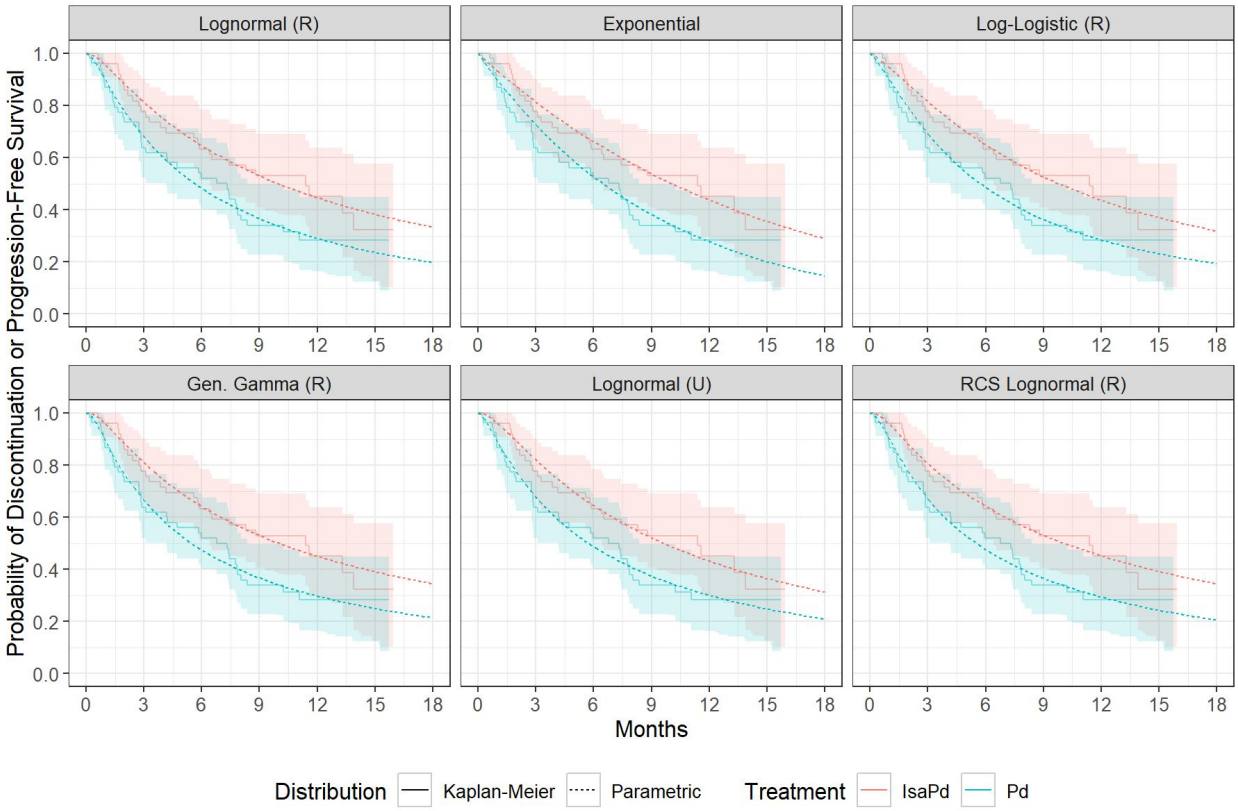
Figure 30: Fit Statistics for parametric distributions fit to PFS on treatment for the 4L population of ICARIA-MM



Abbreviations: BIC: Bayesian Information Criterion (smaller is better); PFS, progression-free survival; R, restricted; RCS, restricted cubic spline; U, unrestricted.

Parametric survival distributions for PFS on treatment during the trial period for the top six best fitting distributions based on BIC are shown in Figure 31 (distributions are ranked by BIC going left to right, top to bottom). All of the top-fitting distributions based on BIC also have relatively good visual fit to the KM curves.

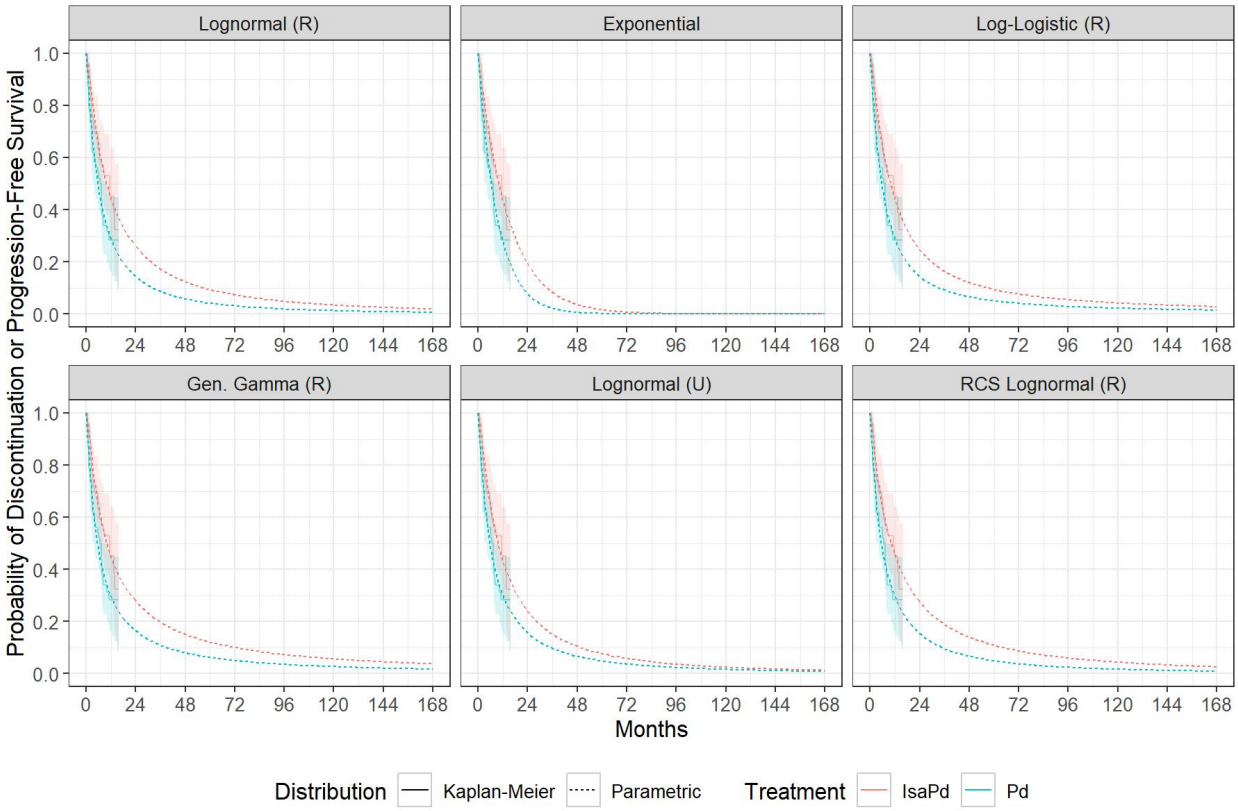
Figure 31: Parametric survival distributions fit to PFS on treatment for the 4L population in ICARIA-MM, by randomised treatment



Abbreviation: PFS, progression-free survival.

Long-term projections of PFS on treatment out to 15 years for these six distributions are shown in Figure 32.

Figure 32: Long-term projections of PFS on treatment based on parametric survival distributions fit to PFS for the 4L population in ICARIA-MM, by randomised treatment



Abbreviation: PFS, progression-free survival.

B.3.3.1.4 Time to Discontinuation

Lacking external data to validate the long-term projections of TTD, the exponential distribution was selected for the base case, as this distribution has the lowest BIC, good visual fit, and the test of linearity of Schoenfeld residuals suggest that the PH assumption (required by exponential distribution) is not violated (Table 38).

Table 38: Parametric distribution used for TTD for IsaPd and Pd

Distribution	Exponential
BIC rank	First
Visual fit	Projection yields good visual fit to the observed KM survival curves
Treatment effect	Test of linearity of Schoenfeld residuals not statistically significant suggesting PH assumption is reasonable
Clinical plausibility	No long-term data to assess clinical plausibility
Comment	RMST at 15 years for IsaPd is at low end of range of estimates and therefore will yield relatively low estimates of costs and favourable ICER for IsaPd

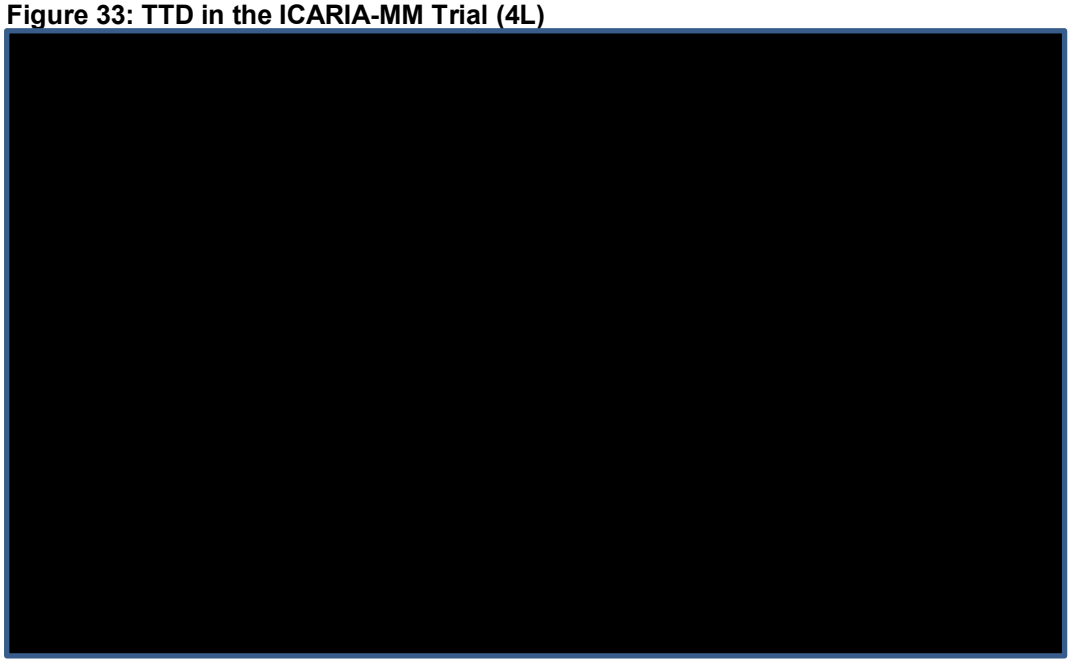
Abbreviations: BIC, Bayesian Information Criterion; ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab, pomalidomide, low dose dexamethasone; KM, Kaplan-Meyer; Pd, pomalidomide, low dose dexamethasone; PH, proportional hazard; R, restricted; RMST, restricted mean survival time; TTD, time to discontinuation.

Rationale for curve selection

- **Kaplan-Meier, ICARIA-MM**

At the time of the cut-off date 27.6% and 45.1% of patients receiving Pd and IsaPd respectively were censored therefore long term parametric extrapolation was needed to estimate TTD over life-time horizon (Figure 33).

Figure 33: TTD in the ICARIA-MM Trial (4L)



Abbreviation: TTD, time to discontinuation

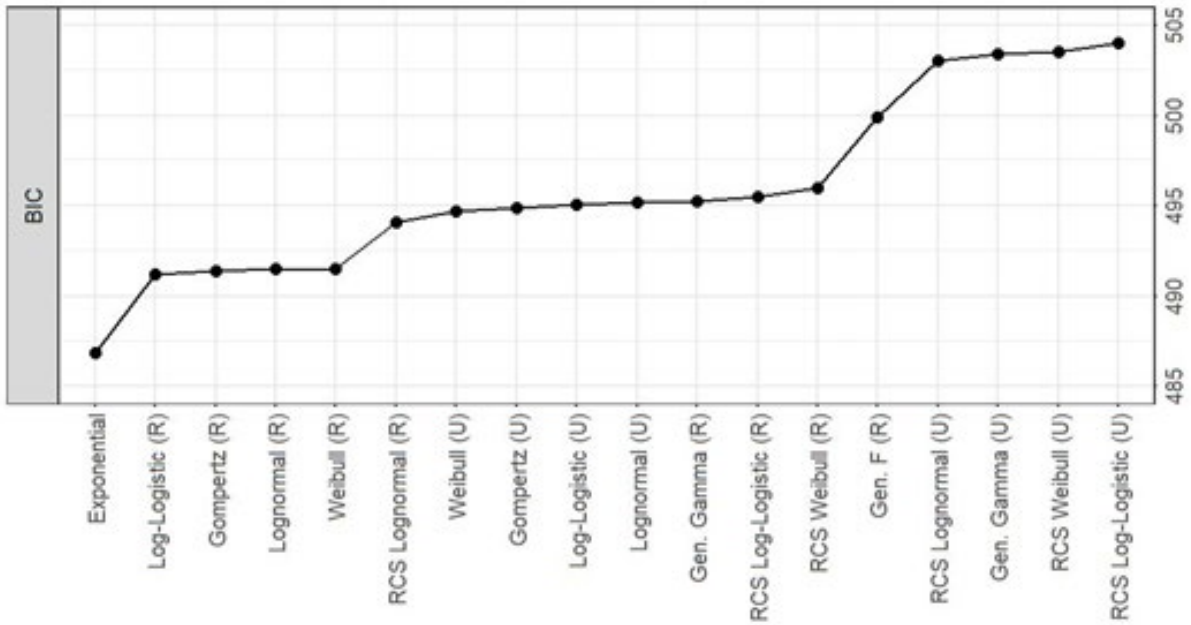
- **Diagnostic and proportional Hazard assumption tests**

KM survival distributions, hazard rates, HRs, Schoenfeld residuals, transformation diagnostics, and treatment effect diagnostics for TTD by treatment group for 4L patients in the ICARIA-MM trial are reported in Appendix K. The hazard rates for the IsaPd and Pd groups oscillate between months 0 and 4, at which point they become more stable. The hazard rates for IsaPd are relatively stable and lower than the hazards for Pd throughout the follow-up period. Although the HR for IsaPd vs Pd generally increases over the follow-up of the trial, the test of non-proportionality is not statistically significant, suggesting PH distributions (exponential, Weibull, Gompertz) are not inappropriate. The cumulative hazard plots are approximately linear suggesting relative constant hazards. The treatment effect diagnostics indicate that PH, proportional odds, and AFT models may all be appropriate.

- **Goodness of fit**

A ranking of parametric distributions fit to TTD by the fit statistics are shown in Figure 34.

Figure 34: Fit statistics for parametric distributions fit to TTD for the 4L population of ICARIA-MM



Abbreviations: BIC: Bayesian Information Criterion (smaller is better); R, restricted; RCS, restricted cubic spline; TTD, time to discontinuation; U, unrestricted.

Parametric survival distributions for TTD during the trial period for the six best fitting distributions based on BIC are shown in Figure 35 (distributions are ranked by BIC going left to right, top to bottom). In visual inspection of the survival distributions, the exponential has a good fit to the Kaplan-Meier curves.

Figure 35: Parametric survival distributions fit to TTD for the 4L population in ICARIA-MM, by randomised treatment

Abbreviation: R, restricted; TTD, time to discontinuation.

Long-term projections of TTD out to 15 years for these six distributions are shown in Figure 36. The exponential distribution shows a steep decline and is below 10% in both arms by 36 months and reaches 0% in both arm by approximately 72 months. As long-term data on TTD for patients receiving IsaPd or Pd are unavailable, it is not feasible to assess the external validity of these projections.

Figure 36: Long-term projections of TTD based on parametric survival distributions fit to TTD for the 4L population in ICARIA-MM, by randomised treatment

Abbreviations: R, restricted; TTD, time to discontinuation.

B.3.3.2 *Adverse reactions*

The model considers the effects of AEs on costs and health-related quality of life (HRQoL). Only Grade 3 or higher AEs with an incidence of 5% or more were considered since AEs not meeting this criterion are unlikely to have any material impact on cost-effectiveness. Probabilities of AEs for patients receiving IsaPd or Pd treatment were based on patients receiving 4L treatment in ICARIA-MM (Table 39).

Table 39: Probabilities of Grade ≥3 adverse events, frequency in ≥5% of patients (4L patients only)

	IsaPd	Pd
Anaemia	0%	2%
Asthenia	2%	3%
Dehydration	0%	0%
Diarrhoea	4%	0%
Fatigue	6%	0%
Febrile neutropenia	14%	5%
Flatulence	0%	0%
Hypokalaemia	2%	0%
Hypophosphatemia	0%	0%
Hypotension	0%	2%
Nausea	0%	0%

Neutropenia	43%	29%
Pneumonia	18%	16%
Sepsis	0%	0%
Septic shock	0%	3%
Thrombocytopenia	6%	10%
Hypercalcaemia	2%	5%
Acute kidney injury	4%	5%

Abbreviations: IsaPd, isatuximab, pomalidomide, low dose dexamethasone; Pd, pomalidomide, low dose dexamethasone.

B.3.3.3 *Clinical expert assessment of applicability of clinical parameters*

A series of interviews with three consultant haematologists was conducted to validate the clinical assumptions applied in the model to ensure they correspond to current clinical pathways and practice in the UK. Three KOLs were invited to participate in telephone interviews using a pre-approved questionnaire based on the model inputs and assumptions. The KOLs were selected based on their experience of treating RRMM patients in the UK. The questionnaire used and the findings of these interviews are provided as a confidential reference (79).

The experts were asked to comment on model structure, baseline patient characteristics, model inputs and assumptions. A key objective of the meeting was to seek feedback on the choice of parametric extrapolation selected for the ICARIA-MM trial.

The choice of appropriate distribution to use for OS and PFS varied between the experts and were not always consistent with their feedback on expected overall survival of RRMM patients. According to the experts, a small proportion of patients may survive over 10 years, and there may be a few patients who survive up to or longer than 15 years. This is clinically valid as RRMM is a heterogeneous disease, and while the majority of patients have poor prognosis (median OS 3-9 months), a small proportion of patients can experience relatively long survival (87, 88). However, it was agreed that 15 years would capture most death events and would be acceptable for the model time horizon.

When selecting extrapolations, 2 out of 3 experts selected Weibull as their preferred choice for OS and one expert selected exponential as his preferred choice. As seen in Figure 24, with Weibull, almost all patients are dead by 5 years on pomalidomide arm and by 10 years on isatuximab. There are no patients alive after 10 years, which is inconsistent with the feedback and published evidence regarding long term for a small proportion of patients.

The exponential curve selected for the base case has the best BIC fit, predicts around 10% alive at 10 years on isatuximab and all patients are dead by 15 years. On pomalidomide, almost all patients are dead by 10 years.

There was no consensus amongst the KOLs on the preferred curve for PFS, however there was a general agreement on the top three curves. The RCS Weibull (R), Weibull (R), and exponential curves appeared to be the preferred options, and one KOL also included Gompertz (R) in the top three. When selecting the distribution for this case,

lognormal (R) was preferred because it provided good visual fit and had the lowest BIC. These are tested in the sensitivity analyses

B.3.3.4 *Transition probabilities*

A partitioned survival model is a type of economic model used to follow a theoretical cohort through time as they move between a set of exhaustive and mutually exclusive heath states. Unlike a Markov model, the number of people in any state at successive points in time is not dictated by transition probabilities. Instead, the model estimates the proportion of a cohort in each state based upon parametric survival equations. These types of model are frequently used to model cancer treatments, with separate survival equations for overall survival and progression-free survival (89). Therefore, transition probabilities are not appropriate in this case.

B.3.4 *Measurement and valuation of health effects*

Multiple myeloma has a drastic impact on patients' quality of life, with each relapse causing a considerable burden on their emotional and physical well-being and social interactions, with an extended effect on their families or carers (7-11). Treatment-related toxicity, accumulating over time, poses an additional burden on patients (35). The effect of coping with the symptoms of MM and the inevitable mortality in the absence of a cure result in poor functioning and mental health problems in many patients (10, 11).

Moreover, relapsed and/or refractory MM can negatively affect the social functioning of patients due to their inability to perform the same level of activities they used to perform and the impact of treatments (increase in frequency of / time spent at hospital / clinic visits) (8). Patients' families also experience emotional and physical burden, having to emotionally deal with the relapsed disease, in addition to undertaking activities the patients cannot do themselves and accompanying them to the hospital/clinic visits (8).

With a view to factoring these patient considerations into the economic appraisal as much as possible, this section sets out the data, methods and assumptions used to measure and value health effects.

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

EQ-5D-5L data from ICARIA-MM were used to derive utility values used in the base case. Utilities have been categorised by health state, with stratification for on and off therapy in the PFS state (Table 40). Health state utility values were estimated using generalised estimating equation (GEE) regression (an extension of generalised linear model regression to adjust for clustering of data). Covariates in these regressions included baseline utility value, treatment group, health state, and on- vs. off-treatment, and proximity to death (e.g., within 84 days of death). Patients could contribute multiple observations to the analysis. To be included in the analysis, patients must have had a baseline assessment and at least one post-baseline assessment. Regressions with a variety of different combinations of these covariates were estimated with the choice of final model determined based on goodness-of-fit statistics and a subjective assessment of clinical plausibility.

Generalised estimating equation regressions were conducted using an identity link function, normal error term distribution, and exchangeable correlation structure with the following covariates for baseline EQ-5D-5L utility value and health state at assessment. Health states included PFS on treatment (treatment-arm specific), PFS off treatment, PPS on treatment and PPS off treatment. PFS off treatment was used as the reference state for the variable coding disease state (note that the choice of the reference level of the covariate has no impact on the predicted utility values). GEE regression was conducted using the SAS PROC GENMOD procedure with the REPEATED statement.

For patients receiving IsaPd or Pd, mean utility values for PFS on treatment generated from ICARIA-MM data were assumed to capture the effects of AEs on HRQoL.

The EQ-5D-5L values by health state are shown below. In line with the NICE reference case, these values are not used in the base case, but are tested in sensitivity analyses. The 3L version is used in the base case and derivation of these are described below.

Table 40: EQ-5D-5L utility values by health state from ICARIA-MM for patients with 3 prior lines of treatments (4L)

	IsaPd	Pd
PFS on Tx	0.801	0.781
PPS on Tx	0.724	0.724
PFS off Tx	0.572	0.717
PPS off Tx	0.650	0.650
Terminal decrement	-0.171	-0.171

Abbreviations: IsaPd, isatuximab, pomalidomide, low dose dexamethasone; Pd, pomalidomide, low dose dexamethasone; PFS, progression-free survival; PPS, post-progression survival, Tx, treatment.

B.3.4.2 *Mapping*

The EQ-5D-5L values (Table 41) were cross walked to EQ-5D-3L values using an algorithm that was developed based on a response mapping approach that estimates the relationship between responses between the EQ-5D-3L and EQ-5D-5L descriptive systems (90). UK tariffs were applied to the mapped 3L scores (91). The results of these are reported in Section B.3.4.5.

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

A SLR to identify relevant HRQoL studies was conducted. See Appendix I for full details on the methods of the SLR and the identified studies. The SLR identified 20 studies (in 26 documents) including 11 non-HTA studies and 9 HTAs. An overview of the 11 non-HTA studies is shown in Appendix I. An overview of the utilities for patients with RRMM reported in the non-HTA studies and HTA studies is provided in Table 41 and Table 42.

Table 41: Utilities for RRMM reported in non-HTA studies

Study reference	Mean utility (SD) for RRMM	Study reference	Mean utility (SD) for RRMM
Borg, 2016 (92)	Pomalidomide + dexamethasone low dose: Stable disease: 0.65 Progressive disease: 0.62 Dexamethasone high dose: Stable disease: 0.61 Progressive disease: 0.59	Moreau 2019 (93)	Baseline: Carfilzomib 70 mg/m^2 plus dexamethasone once weekly: 0.768 (0.196) Carfilzomib 27 mg/m^2 plus dexamethasone twice weekly: 0.769 (0.213) Cycle 15, day 1: Carfilzomib 70 mg/m^2 plus dexamethasone once weekly: 0.813 (n=230) Carfilzomib 27 mg/m^2 plus dexamethasone twice weekly: 0.751 (n=232)
Carlson, 2018 (94, 95)	**Third-line health state utilities:** Progression-free, on treatment: Base case 0.65; Lower 0.52; Upper 0.78 Progression-free, off treatment: Base case 0.72; Lower 0.58; Upper 0.86 Progressed disease: Base case 0.61; Lower 0.49; Upper 0.73 Adverse event disutility: Base case 0.08; Lower 0.07; Upper 0.08	Majer, 2015 (96)	Subgroup with at least 2 prior lines of treatment (n=124): At screening: mean 0.709 (SD 0.201); median 0.752 Using all measurements in subgroup: Panobinostat in combination with bortezomib and dexamethasone (n=374 measurements): mean 0.679 (SD 0.182); median 0.696 Placebo with bortezomib and dexamethasone (n=357 measurements): mean 0.716 (SD 0.201); median 0.747
Cella, 2015 (PREAMBLE) (97)	At month 6, median: 2 lines of prior therapy: 0.69 >2 lines of prior therapy: 0.76 3 lines of prior therapy: 0.76 >3 lines of prior therapy: 0.76	Pelligra, 2017 (98)	Progression-free: 0.73 (lower bound 0.700, upper bound 0.760) Post-progression decrement: -0.054 (lower bound -0.084, upper bound -0.025) Adverse event decrement: -0.049 (lower bound -0.088, upper bound -0.009)
Hatswell, 2019 (99)	Three treatment classes received: Model 1, frequentist meta-regression (all utility values): 0.599 (95% CI 0.568, 0.625) Model 2, frequentist meta-regression (EQ-5D values only): 0.606 (95% CI 0.561, 0.630) Model 3, Bayesian model (all utility values): 0.568 (95%	Jakubowiak, 2017 (100)	**Utilities for the subgroup with >=2 prior therapies are the same as for the whole population.** Progression-free at baseline (cycle 1): carfilzomib plus dexamethasone 0.810; bortezomib plus dexamethasone 0.810 Progression-free (cycle 2): carfilzomib plus dexamethasone

	CrI 0.299, 0.837) Model 4, Bayesian model (EQ-5D values only), preferred approach: 0.578 (95% CrI 0.275, 0.880) Model 5, Bayesian model (EQ-5D values only) with weak priors: 0.603 (95% CrI 0.286, 0.920) Four treatment classes received: Model 1, frequentist meta-regression (all utility values): 0.599 (95% CI 0.403, 0.690) Model 2, frequentist meta-regression (EQ-5D values only): 0.494 (95% CI 0.403, 0.570) Model 3, Bayesian model (all utility values): 0.607 (95% CrI 0.373, 0.842) Model 4, Bayesian model (EQ-5D values only), preferred approach: 0.469 (95% CrI 0.021, 0.918) Model 5, Bayesian model (EQ-5D values only) with weak priors: 0.497 (95% CrI 0.034, 0.958)		0.814; bortezomib plus dexamethasone 0.800 Progression-free (cycle >=3): carfilzomib plus dexamethasone 0.818; bortezomib plus dexamethasone 0.791 Post-progression: carfilzomib plus dexamethasone 0.742; bortezomib plus dexamethasone 0.715 Disutility progression-free, per cycle: carfilzomib plus dexamethasone 0.00015; bortezomib plus dexamethasone 0.00016 Disutility post-progression, per cycle: carfilzomib plus dexamethasone 0.00062; bortezomib plus dexamethasone 0.00062
Reece, 2019 (101)	Subgroup with 2 prior lines of therapy (n=29) Mean change from baseline at cycle 6: -0.03 (CI: -0.111, 0.054)	Weisel, 2018 (102)	Baseline Elotuzumab + pomalidomide + dexamethasone: 0.676 Pomalidomide + dexamethasone: 0.682
Weisel, 2015 (103)	Pomalidomide + dexamethasone low dose: Baseline: 0.63 Best Response: 0.74 Progressive disease (during follow-up): 0.50 Dexamethasone high dose: Baseline: 0.57 Best Response: 0.61 Progressive disease (during follow-up): 0.50		

Abbreviations: CI, confidence interval; EGP, Economic Guidance Panel; EORTC, European Organisation for Research and Treatment of Cancer; EQ, Euroqol; MM, multiple myeloma; PFS, progression-free survival; QLQ, quality of life questionnaire; RRMM, relapsed/refractory multiple myeloma; SD, standard deviation; UK, United Kingdom; VGPR, very good partial response

Table 42: Utilities for RRMM reported in HTA studies

Study reference	Mean utility (SD) for RRMM	Study reference	Mean utility (SD) for RRMM
All Wales Medicines Strategy Group, 2015 (104)	Pre-progression state: 0.65 to 0.75 Post progression state: 0.57 to 0.71 **Sources of data** Utility values were based on a regression analysis performed on EuroQoL five dimensions (EQ-5D) data from the MM-003 study. Grade 3/4 adverse event disutilities (not reported) were based on published estimates or assigned zero disutility if assumed to be transitory or not associated with quality of life impact.	Canadian Agency for Drugs and Technologies in Health, 2016 (105)	Pre-progression: 0.81 **Sources of data** Utility values were taken from a previously published study, identified through a literature review (Agthoven et al, 2004). This Dutch study included previously untreated patients with Stage II/III MM at 6 months after invasive chemotherapy. Utility estimates from the MM-003 trial were used as alternative values in the Economic Guidance Panel (EGP) reanalysis.
National Institute for Health and Care Excellence, 2015 (106, 107)	The overall mean ± SD utility values for the full PANORAMA-1 population Panobinostat in combination with bortezomib and dexamethasone: 0.706 ± 0.192 Bortezomib and dexamethasone: 0.725 ± 0.197 These values were used for the pre-progression on treatment states. Pre-progression without treatment: 0.762 Post-progression (lenalidomide plus dexamethasone and last line of treatment): 0.64 **Sources of data** Quality of life data came from the PANORAMA-1 study. Patients in the PANORAMA-1 trial completed an EORTC QLQ-C30 questionnaire, which was mapped to obtain the corresponding EQ-5D utility value. The utility value for lenalidomide plus dexamethasone was assumed to be the same as that for bortezomib and dexamethasone.	National Institute for Health and Care Excellence, 2016 (108, 109)	In the health state of progression disease • Response: 0.72 • Response and adverse event: 0.65 • Stable disease: 0.63 • Stable disease and adverse event: 0.55 • Progressive disease: 0.58 • Progressive disease and adverse event: 0.51 • Stable disease and hospitalisation: 0.49 In the health state of non-progression disease • Response: 0.76 • Response and adverse event: 0.68 • Stable disease: 0.66 • Stable disease and adverse event: 0.59 • Progressive disease: 0.62 • Progressive disease and adverse event: 0.54 • Stable disease and hospitalisation: 0.53 **Sources of data**

			The EQ-5D UK tariff was applied to the data obtained from the EQ-5D in the MM-003 trial. Multivariate analysis was then conducted to determine the most significant predictors of HRQoL over all time points.
National Institute for Health and Care Excellence, 2017 (110, 111)	Utility (95% CI) Very good partial response (VGPR+) health state - VGPR+: 0.712 (0.69 to 0.732) Partial response pre-progression health state - partial response: 0.674 (0.609 to 0.729) Stable disease pre-progression health state - stable disease: 0.653 (0.579 to 0.714) Progressed disease post-progression health state - progressed disease: 0.654 (0.587 to 0.711) VGPR+ (pre-progression health state) Adverse event: 0.696 (0.648 to 0.737) New primary malignancy: 0.412 (0.299 to 0.507) Hospitalisation: 0.641 (0.425 to 0.776) ≤3 months until end of life: 0.580 (0.469-0.667) Partial response (pre-progression health state) Adverse event: 0.658 (0.567 to 0.733) New primary malignancy: 0.375 (0.218 to 0.504) Hospitalisation: 0.604 (0.344 to 0.773) ≤3 months until end of life: 0.542 (0.388 to 0.664) Stable disease (pre-progression health state) Adverse event: 0.636 (0.537 to 0.718) New primary malignancy: 0.353 (0.188 to 0.488) Hospitalisation: 0.582 (0.315 to 0.757)	National Institute for Health and Care Excellence, 2017 (41, 112)	Pre−progressive disease: 0.61 (CI: 0.59 to 0.63) Progressive disease: 0.57 (CI: 0.55 to 0.59) Adverse events (CI) • Febrile neutropenia: −0.39 (−0.24 to −0.55) • Neutropenia: −0.15 (−0.09 to 0.21) • Anaemia: −0.31 (−0.20 to 0.44) • Thrombocytopenia: −0.31 (−0.20 to 0.44) • Lymphopenia: −0.07 (−0.04 to −0.09) • Leukopenia: −0.07 (−0.04 to −0.09) • Upper respiratory infection (all grades): −0.19 (−0.12 to −0.27) • Pneumonia: −0.19 (−0.12 to −0.27) • Hypophosphatemia: −0.07 (−0.04 to −0.09) • Nausea (all grades): −0.10 (−0.07 to −0.15) • Diarrhoea: −0.10 (−0.07 to −0.15) • Fatigue: −0.12 (−0.07 to −0.16) • Asthenia: −0.12 (−0.07 to −0.16) • Dyspnoea: −0.12 (−0.07 to −0.16) • Back pain: −0.07 (−0.04 to −0.09) • Peripheral neuropathy (all grades): −0.10 • Flatulence: 0.00 (0 to 0) • Abdominal Pain: −0.05 (−0.03 to −0.07) • Abdominal distention: −0.05 (−0.03 to −0.07) • Hypokalaemia: −0.20 • Dehydration: 0.00 (0 to 0) • Hypotension: −0.07 • Septic Shock: −0.20 (−0.12 to −0.28) • Syncope: −0.10 • Sepsis: −0.20 (−0.12 to −0.28)

	≤3 months until end of life: 0.521 (0.359 to 0.648) Progressed disease (post-progression health state) New primary malignancy: 0.355 (0.196 to 0.486) Hospitalisation: 0.584 (0.322 to 0.755) ≤3 months until end of life: 0.522 (0.366 to 0.646) Treated related adverse events: utility decrement (mean duration, weeks) Anaemia: -0.016 (6.01) Cardiac failure: -0.016 (1.62) Deep vein thrombosis: -0.016 (1.63) Diarrhoea: -0.016 (4.49) Fatigue: -0.016 (9.05) Upper respiratory tract infection/Pulmonary-related: -0.016 (2.20) Ischemic heart disease: -0.016 (0.60) Nausea: -0.016 (2.94) Neutropenia: -0.016 (2.15) Peripheral neuropathy: -0.016 (7.14) Pneumonia: -0.016 (2.80) Pulmonary embolism: -0.016 (8.08) Rash-related: -0.016 (3.73) Renal failure: -0.016 (5.29) Thrombocytopenia: -0.016 (3.02) Vomiting: -0.016 (0.68) New primary malignancy flag: -0.300 (5.76) Per cycle utility decrements associated with treatment related adverse events Lenalidomide+dexamethasone: -0.00115		**Sources of data** MM−003 trial (reported by Palumbo)

	Ixazomib+lenalidomide+dexamethasone: -0.00157 Bortezomib+dexamethasone: -0.00350 **Sources of data** TMM1 trial		
Scottish Medicines Consortium, 2010 (113)	Patients with stable disease: 0.81 Partial responders: 0.81 Complete responders: 0.81 **Sources of data** From a published study not cited	Scottish Medicines Consortium, 2016 (114)	Pre-progression on treatment Panobinostat: 0.679 Lenalidomide: 0.716 Pre-progression off treatment (panobinostat or lenalidomide): 0.720 Post-progression: 0.64 **Sources of data** Utilities for the pre-progression health state for the panobinostat regimen and the lenalidomide regimen were based on QLQ-C30 quality of life data from the PANORAMA-1 study, which were mapped to EQ-5D to derive utility values. The utility values for the pre-progression, off treatment and post-progression health states were taken from published literature.
Scottish Medicines Consortium, 2017 (115)	Health states within PFS • Response to treatment: 0.75 • Stable disease: 0.65 Health states within the progressive disease condition • Response: 0.71 • Stable disease: 0.62 • Progressive disease: 0.57 **Sources of data** Health state utilities based on the EQ–5D were derived from the MM-003 study.		

Abbreviations: CI, confidence interval; EGP, Economic Guidance Panel; EORTC, European Organisation for Research and Treatment of Cancer; EQ, Euroqol; MM, multiple myeloma; PFS, progression-free survival; QLQ, quality of life questionnaire; RRMM, relapsed/refractory multiple myeloma; SD, standard deviation; UK, United Kingdom; VGPR, very good partial response

B.3.4.4 *Key differences in trial utilities vs published utilities*

Of the studies published in the literature, Cella et al 2015 reports utilities in patients with 3 prior therapies treated with IMID and PI. At 6 months, the utility for patients responding to treatment is 0.76. All other studies retrieved were not specific to 4L RRMM patients.

The HTA submissions provide more information on utilities for RRMM. In general, for those treatments currently recommended by NICE in patients with 3 prior therapies including both lenalidomide and bortezomib (TA427, TA510, TA505, TA380) (3, 4, 39, 61) (Table 43).

Table 43: Utilities for patients with RRMM

<table>
<tr><th>Regimen</th><th>Utility values</th></tr>
<tr><td>Pomalidomide, in combination with low-dose dexamethasone (4) †</td><td>• Based on EQ-5D-3L reported in MM-003 trial
<table>
<tr><th>Best overall response</th><th>Within PD health state</th><th>Hospitalisation or adverse event</th><th>Utility</th></tr>
<tr><td>Response</td><td>X</td><td>X</td><td>0.75</td></tr>
<tr><td>SD</td><td>X</td><td>X</td><td>0.65</td></tr>
<tr><td>PD</td><td>X</td><td>X</td><td>0.61</td></tr>
<tr><td>SD</td><td>X</td><td>Hospitalisation</td><td>0.52</td></tr>
<tr><td>Response</td><td>√</td><td>X</td><td>0.71</td></tr>
<tr><td>SD</td><td>√</td><td>X</td><td>0.62</td></tr>
<tr><td>PD</td><td>√</td><td></td><td>0.57</td></tr>
<tr><td>SD</td><td>√</td><td>Hospitalisation</td><td>0.48</td></tr>
<tr><td colspan="4">Key: SD stable disease, PD progressive disease</td></tr>
</table></td></tr>
<tr><td>Daratumumab monotherapy (41)</td><td>• Pre-progressive disease: 0.61
• Progressive disease: 0.57</td></tr>
<tr><td>Panobinostat in combination with bortezomib and dexamethasone (39)</td><td>• Pre-progression on treatment: 0.706
• Pre-progression no treatment: 0.762
• Post progression: 0.64</td></tr>
</table>

†based on EQ-5D-3L.

In general, the utility data reported in ICARIA-MM appear to be higher (better) than that previously reported in other HTAs.

Progression-free (off treatment) in ICARIA-MM is 0.473 on IsaPd and 0.621 on Pd based on mapping EQ-5D-5L to EQ-5D-3L (Table 44). This difference between IsaPd and Pd may be due to AEs or concerns from being taken off IsaPd. However, both these values are lower than that reported in panobinstat NICE submission (TA380) (81) for pre-progression without treatment (0.762). Post-progression utility was also lower in this submission compared to ICARIA-MM.

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

B.3.4.5.1 Health state utilities for IsaPd and comparators

In line with the NICE reference case, utility estimates derived from mapping the EQ-5D-5L to 3L version was used in the cost-effectiveness analysis. The model considered a terminal decrement of 0.204 QALY, lasting over a period of 12 weeks (Table 44).

Table 44: EQ-5D-3L utility values by health state (4L) used in the cost-effectiveness analysis (mapped from EQ-5D-5L)

State	Utility	95%CI	SE
PFS on treatment (IsaPd)	0.731	0.695, 0.768	0.018
PFS off treatment (IsaPd)	0.473	0.288, 0.658	0.095
PFS on treatment (Pd)	0.717	0.677, 0.758	0.021
PFS off treatment (Pd)	0.621	0.527, 0.714	0.048
PPS on treatment	0.649	0.591, 0.707	0.030
PPS off treatment	0.553	0.478, 0.629	0.038
Terminal decrement	−0.204	−0.326, −0.083	0.062

Abbreviations: CI, confidence interval; EQ-5D-3L (5L), Euro QoL Group self-report questionnaire with 3 (5) dimensions and 3 (5) levels per dimension; IsaPd, isatuximab, pomalidomide, low dose dexamethasone; Pd, pomalidomide, low dose dexamethasone; PFS, progression-free survival; SE, standard error.

B.3.4.5.2 Disutilities for adverse events

For patients receiving IsaPd or Pd, mean utility values for PFS on treatment generated from ICARIA-MM data were assumed to capture the effects of AEs on HRQoL.

B.3.4.5.3 General population utility values

Age- and gender-matched general population utilities were used to adjust utility values for age-related declines in HRQoL. These utilities were based on published UK population norms (116). General population values were used as a ceiling estimate such that no estimates from ICARIA-MM ever exceeded general population utility values. Regression coefficients used to estimate general population utility values are provided in Table 45.

Table 45. Coefficients of regression analysis

Regression analysis	Value
Intercept	0.9508566
Covariates	
Male vs female	0.0212126
Age coefficient	−0.0002587
Age-squared coefficient	−0.0000332

B.3.4.6 *Clinical expert assessment of applicability of health state utility values*

The clinical experts who participated in the validation process for the model inputs (Section B.3.3.3) were asked to comment on the utilities derived from the ICARIA-MM trial for IsaPd and Pd (79).

According to the experts, it was reasonable that patients in the PFS off-treatment state could have a lower QoL than:

- Patients in the PFS on-treatment state, as discontinuations may be due to severe adverse events
- Patients in the PPS on-treatment state (i.e. patients who have progressed but are still on study treatment), as patients have started to progress but not progressed enough clinically to warrant discontinuation.
- Patients in the PPS off-treatment state (i.e. who have progressed and are on a post-progression therapy [defined as PPS off-Tx in the KOL interview guide]) – however, this is only if patients respond to their post-progression therapy
- Palliative patients should have the lowest QoL – lower than PPS (on study treatment or post-progression therapy), and lower than PFS off-treatment

The details of this process have been described previously in Section B.3.3.3.

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

B.3.5.1 *Resource identification, measurement and valuation studies*

An SLR was undertaken to identify relevant resource use data for patients with RRMM in England. For full details on the methods of the SLR and the identified studies, see Appendix J. The SLR identified 41 studies (in 53 documents) (Appendix J).

41 studies (in 53 documents) were found in the SLR of resource use and costs data of which National Institute for Health and Care Excellence (NICE, 4), the Scottish Medicines Consortium (SMC, 4), and the All Wales Medicines Strategy Group (AWMSG, 1) in which resource use and/or cost data used in the models were described and one published retrospective audit set in UK hospital. For this section of the submission, we report a summary of the UK based evidence. The remaining identified studies are described in Appendix J.1.1.

Of the 41 studies identified in this SLR, forty were not used directly in the submission. In Table 46 below we report on the four NICE HTA submissions relevant to RRMM. One published HTA (TA510, daratumumab monotherapy) has been used to inform this submission. Information on resource utilisation for routine monitoring in the health states, duration of adverse events and post-study treatments as described in the TA510 were also used in our submission. The costs associated with resource utilisation and adverse events were updated using NHS reference costs 2018-2019. Details of this study are shown below. Full details on the remaining studies are reported in Appendix J.

Table 46: Studies reporting resource data

Study, Year, Country	Applicability to clinical practice in England	Cost valuations used in study	Costs for use in economic analysis	Technology costs
Documents produced by UK HTA agencies: NICE				
National Institute for Health and Care Excellence 2015 (106, 107) UK	Applicable	**DIRECT COSTS** £, price year not reported Panobinostat, per 20 mg tablet: £776 Cost, per 3-week cycle Panobinostat in combination with bortezomib and dexamethasone, first treatment phase, cycles 1 to 8: £5,375 Panobinostat in combination with bortezomib and dexamethasone, second treatment phase, cycles 9 to 16: £4,566 Bortezomib and dexamethasone, first treatment phase, cycles 1 to 8: £1,847 Bortezomib and dexamethasone, second treatment phase, cycles 9 to 16: £923 Lenalidomide: £2,830 Pomalidomide: £6,097 Fourth-line therapy (other active treatments): £1,001 Medical-resource utilisation: £2,188 Unit costs per monitoring activity Serum protein assessment: £15 Skeletal survey (bone X-ray): £75.00 Lab results - Haematology: £3.00 Lab results - Thyroid function test: £18.00 Lab results - Blood chemistry: £3.00 Specialist visit £156.00 Health-state unit costs Pre-progression Panobinostat in combination with bortezomib and dexamethasone, cycle 1 to 8: £6,293 Panobinostat in combination with bortezomib and dexamethasone, cycle 9 to 16: £5,176 Bortezomib and dexamethasone, cycle 1 to 8: £2,763 Bortezomib and dexamethasone, cycle 9 to 16: £1,533	Not used directly in submission	Not used directly in submission

Study, Year, Country	Applicability to clinical practice in England	Cost valuations used in study	Costs for use in economic analysis	Technology costs
		Pre-progression, no treatment Monitoring costs: £92.78 Post-progression Lenalidomide and dexamethasone: £2,831.69 Concomitant medication: £95.20 Pomalidomide and dexamethasone: £6,098.63 Concomitant medication: £67.89 Other active treatments: £1,001 Best supportive care: £2,188 Death Terminal care, lump sum applied on death: £1,235		
National Institute for Health and Care Excellence 2016 (108, 109) UK	Applicable	**DIRECT COSTS** Pomalidomides 21-tablet pack (excluding VAT): £8,884 Average cost of a course of treatment: £44,420 Unit cost of one red blood cell unit: £121.85 Unit cost of a platelet transfusion: £196.961 Average cost for the last 8 weeks prior to a patient dying: £5,363	Not used directly in submission	Not used directly in submission
National Institute for Health and Care Excellence 2017 (41, 112)	Applicable	**DIRECT COSTS (2014/2015)** Drug cost (per pack/vial) Daratumumab 100mg: £360.00 Daratumumab 400mg: £1,440.00 Pomalidomide 4mg: £8,884.00 Dexamethasone 2mg: £78.00 Panobinostat 10mg: £3,492.00 Panobinostat 15mg: £3,492.00 Panobinostat 20mg: £4,656.00 Bortezomib 4mg: £217.82 Bendamustine 25mg: £347.26 Bendamustine 100mg: £1,379.04	The resources used during routine monitoring in the health states have been used directly in our submission. The units used are based on KOL input (79). AEs event duration have	Not used directly in submission

Study, Year, Country	Applicability to clinical practice in England	Cost valuations used in study	Costs for use in economic analysis	Technology costs
		Administration costs Daratumumab: £4,437.39 Bortezomib: £762.38 Bendamustine 25mg: £991.33 Bendamustine 100mg: £388.51 Daratumumab (1st dose only): £414 Daratumumab (all subsequent complex infusions): £362 Pomalidomide plus dexamethasone (1st dose only): £192 Panobinostat (1st dose only): £192 Bortezomib (per dose): £257 Bendamustine 1st dose only): £414 Bendamustine (all subsequent complex infusions): £362 Other health state costs Physician visit: £162.02 Complete blood test: £3.01 Blood chemistry: £1.19 Adverse events costs Febrile neutropenia: £6,697.31 Neutropenia: £1,096.05 Anaemia: £788.00 Thrombocytopenia: £617.55 Lymphopenia: £1,096.05 Leukopenia: £1,096.05 Upper respiratory infection (all grades): £759.21 Pneumonia: £1,965.45 Hypophosphatemia: £1,249 Diarrhoea: £1,165 Nausea (all grades): £727.55 Fatigue: £727.55 Asthenia: £727.55 Dyspnoea: £216.66 Back pain: £863.18 Peripheral neuropathy (all grades): £643.85	also been used in our submission. In each case the most up-to-date NHS reference costs have been applied. Both the above have been tested in sensitivity analyses using KOL input	

Study, Year, Country	Applicability to clinical practice in England	Cost valuations used in study	Costs for use in economic analysis	Technology costs
		Abdominal Pain: £2,410 Hypokalaemia: £1,249 Hypotension: £1,096 Sepsis: £2,973 Resource utilisation Rate per week by health state: *Progression free survival (PFS) (on treatment); PFS (off treatment); post-progression survival (PPS), subsequent active treatment; PPS, best supportive care* Physician visit: 0.23; 0.08; 0.08; 0.08 Complete blood count test: 0.21; 0.21; 0.39; 0.39 Biochemistry: 0.19; 0.19; 0.33; 0.33		
National Institute for Health and Care Excellence 2017 (110, 111) UK	Applicable	**DIRECT COSTS (2014/2015)** Drug cost (per pack/vial) Lenalidomide 25mg: £4,368.00 Dexamethasone 40mg: £49.00 Ixazomib 4mg: £6,336.00 Hospitalisation costs Acute ward - per event: £1,119.89 ICU ward - per event: £1,306.16 Palliative ward - per event: £186.56 Hospice - per day: £160.46 End of Life Care per decedent: £10,670 Adverse events (secondary care; primary care; weighted average) Anaemia: £1,145; £46; £1,036 Cardiac failure: £2,038; £46; £2,038 DVT: £627, £46, £622 Diarrhoea: £1,120; £46; £1,087 Fatigue: £1,120; £46; £46 Upper respiratory tract infection/Pulmonary-related: £1,127; £46; £586 Ischemic heart disease: £1,700; £46; £873 Nausea: £1,120; £46; £46 Neutropenia: £715; £46; £400	Not used directly in the submission	Not used directly in the submission

Study, Year, Country	Applicability to clinical practice in England	Cost valuations used in study	Costs for use in economic analysis	Technology costs
		Peripheral neuropathy: £1,253; £46; £1,008 Pneumonia: £2,066; £46; £2,066 Pulmonary embolism: £1,571; £46; £1,571 Rash-related: £1,120; £46; £46 Renal failure: £1,571; £46; £1,571 Thrombocytopenia: £643; £46; £402 Vomiting: £1,120; £46; £1,087 New primary malignancy: £1,927; £46; £1,927 Unit costs for other direct costs (visits and tests) Outpatient visit to oncologist: £158.54 Complete blood count: £3.01 Blood testing-chemistry panel: £1.19 Clinical Biochemistry: £5.49 Blood testing-immunofixation: £5.49 Blood testing-serum protein electrophoresis: £1.19 Bone testing - X-rays: £69.03 Bone marrow aspirate / biopsy: £497.23 C-reactive protein: £5.49 Serum albumin: £1.19 Serum lactate dehydrogenase: £1.19 Serum ß2 microglobulin (S ß2M): £1.19 Urine testing - immunofixation: £6.99 Urine testing - protein electrophoresis: £6.99 Transthoracic echocardiogram (applied to patients receiving panobinostat plus bortezomib plus dexamethasone only): £83.94 **Resource use** **Routine care resource use: number for first treatment cycle; number for subsequent treatment cycles** Outpatient visit to oncologist: 3; 1 Complete blood count: 1; 2 Blood testing-chemistry panel: 1; 2 Blood testing-immunofixation: 1; 0 Blood testing-serum protein electrophoresis: 1; 0 Bone testing - X-rays: 1; 0		

Study, Year, Country	Applicability to clinical practice in England	Cost valuations used in study	Costs for use in economic analysis	Technology costs
		Bone marrow aspirate/biopsy: 1; 0 C-reactive protein: 1; 0 Serum albumin: 1; 0 Serum lactate dehydrogenase: 1; 0 Serum ß2 microglobulin (S ß2M): 1; 0 Urine testing - immunofixation: 1; 0 Urine testing - protein electrophoresis: 1; 0 Transthoracic echocardiogram (applied to patients receiving panobinostat plus bortezomib plus dexamethasone only): 1; 0		

Abbreviations: AE, adverse event; AWMSG, All Wales Medicines Strategy Group; CBC, complete blood cells; CIK, Cytokine-Induced Killer (cells); CNS, central nervous system; CT, computerised tomography; DR, double relapsed or refractory; DRMM, double relapsed or refractory multiple myeloma; DVT, deep vein thrombosis; ICU, intensive care unit; MM, multiple myeloma; MRI, magnetic resonance imaging; PET, positron emission tomography; PFS, progression-free survival; PPS, post-progression survival; RRMM, relapsed or refractory multiple myeloma; SD, standard deviation; SEK, Swedish Krona; UK, United Kingdom; US, United States of America; VAT, Value Added Tax; WBC, white blood cell.

B.3.5.1.1 Appropriateness of NHS Ref costs/PbR tariffs

NHS reference costs (2017–2018) have been used to inform cost inputs for administration costs, monitoring costs and adverse event management.

B.3.5.1.2 Clinical expert assessment of applicability of cost and healthcare resource use values

Expert opinion was sought to validate the resource utilisation for routine monitoring, post study treatments and duration of adverse events. The resource utilisation for monitoring requirements in the progression-free and post-progression states have been implemented in the base case. The duration of AEs and post study treatments were tested in the sensitivity analyses, as there was variation in the KOL responses for these inputs. The details of this process have been described previously above, and full details are available as data on file (79).

B.3.5.2 *Intervention and comparators' costs and resource use*

Medication costs and medication and administration costs are calculated by multiplying estimates of TTD in each model cycle with corresponding estimates of medication costs and medication administration costs in each cycle. These costs are then discounted and summed across all model cycles. Additional details regarding the calculation of medication costs and medication administration costs in each cycle are provided below.

For any given model cycle, medication costs are calculated by multiplying expected number of days of medication received during the cycle by the cost of medication per day of use. The expected days of use per cycle were based on prescribing information (Table 47). For therapies dosed based on body surface area (BSA) or weight, the planned dose per cycle of use was estimated by multiplying the prescribed dose strength per m^2 of BSA/per kg of body weight by the estimated mean BSA/mean body weight observed in ICARIA-MM. For medications dosed based on weight or BSA, unused medication was assumed to be discarded. Medication costs were adjusted for differences between planned and actual doses received based on drug-specific estimates of relative dose intensity (RDI) obtained from ICARIA-MM for IsaPd and Pd.

Table 47: Medication dosing

Regimen	Drug	Cycle	Daily dose	Days dosed per cycle	Weeks per model cycle	Maximum cycle	Relative dose intensity
IsaPd†	Isatuximab	1	10 mg/kg	4	4	1	[redacted]
		2+	10 mg/kg	2	4		
	Pomalidomide	All	4 mg/day	21	4		
	Dexamethasone (w/Pom)	All	40 mg/day	4	4		[redacted]
Pd‡	Pomalidomide	All	4 mg/day	21	4		86.63%
	Dexamethasone (w/Pom)	All	40 mg/day	4	4		86.63%

†Source: ICARIA-MM (44), Sarclisa Draft Summary of Product Characteristics, see Appendix C.1
‡Source: Imnovid Summary of Product Characteristics (117)

Unit costs of medications other than isatuximab were obtained from the current versions of the British National Formulary (BNF) and the drugs and pharmaceutical electronic market information tool (eMIT) (Table 48). The patient access scheme (PAS) discounts for isatuximab as agreed by PASLU have been applied in the base case. Discounts for pomalidomide and panobinostat have been assumed for the purposes of the model – it is tested in the sensitivity analysis.

Table 48: Unit costs of medication costs

Drug	Cost per pack (£)	PAS Discount (%)	Units per pack	mg per unit
Isatuximab	[redacted]	[redacted]	1	100
Pomalidomide	8,884.00†	[redacted]	21	4
Dexamethasone, oral	200†		10	80

†Source: BNF (118) ‡ Assumed. Abbreviation: PAS, patient access scheme.

B.3.5.3 *Costs of administration*

Administration costs were assigned for every day of medication administration. Costs per administration/dispensation were based on NHS Reference costs (cost year: 2017-2018) as summarised in Table 49.

Table 49. Administration costs

Type of administration	NHS Reference Code	Cost (£)†
Oral, first dose	SB11Z	131.61
Oral, subsequent dose(s)	-	0‡
Injection, first dose	SB12Z	174.40
Injection, subsequent dose(s)	SB12Z	174.40
IV, first dose	SB13Z	228.56
IV, subsequent dose(s)	SB15Z	233.23
IV, prolonged first dose	SB14Z§	313.44

Abbreviations: IV, intravenous; SPC, summary of product characteristics. †Source: NHS Reference Costs (119). ‡Assumed to have a cost of zero, based on daratumumab submission. § NHS reference cost used for the first administration of daratumumab monotherapy, in line with its SPC.

SB13Z (£228.56) is used for the first isatuximab dose in cycle 1. All subsequent doses of isatuximab use SB15Z (£233) per administration. For pomalidomide SB11Z (£132) is used for the first dose only. Subsequent doses of pomalidomide have zero cost, as this is an oral treatment.

Based on NHS pharmacist feedback, for regimens with multiple drugs, the maximum administration cost associated with the drugs in the regimen was used for any given weekly cycle. Therefore, for the combination of IsPd, the highest administration costs corresponding to the SB13Z is applied for the administration of the combination IsaPd at cycle 1. Thereafter SB15Z is applied to all subsequent cycles. SB14Z is used for the first administration of daratumumab monotherapy (based on prolonged first infusion); thereafter SB15Z is applied to all subsequent cycles of daratumumab.

B.3.5.4 *Premedication treatments*

Patients receiving Pd or IsaPd were assumed to receive acetylsalicylic acid with every dose of Pd. Unit costs of the concomitant medications were based on eMIT (120) (Table 50). While included in the model for completeness, these costs are not material relative to the costs of other medications.

Table 50: Costs for premedication's

Drug	Cost per pack[†]	mg per unit
Corticosteroid (methylprednisolone IV)	£4.75	125
Antipyretic (acetaminophen)	£0.74	500
Antihistamine (cetirizine hydrochloride)	£0.16	10
Acetylsalicylic acid	£0.47	75

†Source: eMIT (120)

B.3.5.5 *Concomitant treatments*

The model assumes that patients receiving IsaPd and Pd may also receive prophylactic granulocyte colony stimulating factor (GCSF), red blood cell (RBC) transfusions, and platelet transfusions. The unit costs of concomitant treatments were based on NHS Reference Costs (Table 51). The mean number of units per patient were based on estimates used in the economic model in the manufacturer's submission to NICE for the STA of Dara (TA510), which were based on efficacy analyses conducted by the manufacturer (Table 51) (41). For patients receiving Pd, the proportions of patients receiving concomitant treatments were from the economic model in the manufacturer's submission to NICE for the STA of Pd (TA427) (Table 51) (40). For patients receiving IsaPd, the use of these treatments was assumed to be the same as that for Pd. The expected costs of subsequent treatments were assigned as a one-off cost at therapy initiation.

Table 51: Unit costs, mean number of units per patients, and percent of patients receiving concomitant treatments

			Percent of patients receiving concomitant treatments by regimen	
Treatment	**Unit Cost (£)[†‡]**	**Mean number per patient[†§]**	**IsaPd[¶]**	**Pd[¶]**
GCSF	52.70	1.00	43%	43%
RBC transfusion	121.85	3.00	49%	49%
Platelet transfusion	196.96	4.79	20%	20%

Abbreviations: GCSF, granulocyte colony stimulating factor; IsaPd, isatuximab, pomalidomide, low dose dexamethasone; Pd, pomalidomide, low dose dexamethasone; RBC, red blood cell.
†Source: Daratumumab NICE STA (41). ‡NHS Reference Costs (119). §Janssen, from TA510 (41). ¶Pd, TA427, Committee Papers (40)

B.3.5.6 *Health-state costs and resource use*

B.3.5.6.1 Costs of follow-up and monitoring

Follow-up and monitoring costs were computed by multiplying unit costs of services by utilisation during PFS on treatment, PFS off treatment, PPS on treatment, and PPS off

treatment. Costs associated with follow-up and monitoring are based on estimates used in the Dara NICE submission (41), where costs were adjusted to reflect current NHS reference costs (119) (Table 52).

Table 52: Unit costs of follow-up and monitoring services

Service	Cost (£)†
Physician visit	160.00
Complete blood count test	3.00
Biochemistry	1.00

†Source: Daratumumab NICE STA (41)

Based on our discussions with clinicians, it was assumed that each follow-up and monitoring service occurs at a frequency of once per month. All patients were assumed to receive follow-up and monitoring services during PFS. To compute follow-up and monitoring costs during the PPS on treatment and PPS off treatment periods, the model takes as inputs the proportion of patients in post-progression that are on treatment as well as the duration of the PPS on treatment period (Table 53). Patients allocated to the PPS on treatment group receive the follow-up and monitoring costs for the mean duration in PPS on treatment. The remaining patients in PPS receive the costs associated with the PPS off treatment state. Estimates for percent of progressing patients on therapy post-progression and mean duration of post-progression treatment were based on data from ICARIA-MM.

Table 53: Post progression treatment data

Regimen	% of progressing patients on-therapy post-progression	Mean duration of post-progression treatment (months)
IsaPd	73.9%	2.29
Pd	72.7%	1.54

Abbreviations: IsaPd, isatuximab, pomalidomide, low dose dexamethasone; Pd, pomalidomide, low dose dexamethasone.

B.3.5.6.2 Terminal care costs

End of life care costs for patients with RRMM (£894.15) were estimated using the value reported in the manufacturer's submission on pomalidomide to NICE (TA427) (4) and updated to 2018 costs using the NHS inflator (119).

B.3.5.7 *Adverse reaction unit costs and resource use*

B.3.5.7.1 Costs of treating adverse events

The expected cost of AEs per patient was calculated by multiplying the estimated probability of each AE by corresponding estimates of the expected cost per AE then summed across AEs. The probabilities of AEs were described above (Table 39). The expected costs per AEs were estimated using NHS 2017/2018 reference costs (119, 121) (Table 54). The expected costs of AEs per patient were assigned as a one-off cost at therapy initiation.

Table 54: Estimated costs associated with adverse events

Adverse Event	NHS Code(s)	Estimated Cost

		(£)†
Abdominal distension	FD05A	2,362.11
Abdominal pain	FD05A	2,362.11
Anaemia	Weighted average of: SA04G, SA04H, SA04I, SA04J, SA04K, SA04L	691.09
Asthenia	Clinic visit	727.55
Diarrhoea	Weighted average of: FD10J, FD10K, FD10L, FD10M	546.61
Fatigue	Clinic visit	727.55
Febrile neutropenia	PMA45A-D	7,230.00
Hypokalaemia	Weighted average of: KC05J, KC05K, KC05L, KC05M, KC05N	435.50
Hypophosphatemia		435.50
Hypotension	Weighted average of: SA08G, SA08H, SA08J	1,077.36
Lymphopenia	Weighted average of: SA08G, SA08H, SA08J	1,077.36
Nausea	Clinic visit	727.55
Neutropenia	Weighted average of: SA08G, SA08H, SA08J	1,077.36
Pneumonia	Weighted average of: DZ11K, DZ11L, DZ11M, DZ11N, DZ11P, DZ11Q, DZ11R, DZ11S, DZ11T, DZ11U, DZ11V	1,784.00
Sepsis	Weighted average of: WH07C, WH07D	3,997.10
Septic shock		3,997.10
Thrombocytopenia	Weighted average of: SA12G, SA12H, SA12J, SA12K	640.09
Hypercalcaemia	Weighted average of: KA03C, KA03D	4,098.18
Acute kidney injury	Weighted average of: LA07H, LA07J, LA07K	1,447.87

†Source: NHS Reference Costs (119)

B.3.5.8 *Miscellaneous unit costs and resource use*

B.3.5.8.1 Cost of subsequent treatments

For each comparator, expected costs of subsequent treatments were computed by multiplying the proportion of patients receiving each treatment by corresponding expected cost per course of treatment and then summing across all subsequent treatments. The expected cost per course of subsequent treatment was calculated using methods similar those used for initial treatment. Expected costs of subsequent treatments were assigned as a one-off cost at the time of discontinuation of initial treatment.

Because of the large number of different subsequent treatments received, only the ten most frequently received treatments in ICARIA-MM were included in the models. The utilisation of subsequent therapies for IsaPd and Pd were based on data on the 4L population in ICARIA-MM (Table 55).

Table 55: Proportion of patients receiving top ten subsequent anti-cancer treatments from ICARIA-MM trial

Treatment	IsaPd	Pd
Bendamustine	10.71%	11.90%
Bortezomib	25.00%	16.67%
Carfilzomib	17.86%	21.43%
Daratumumab	7.14%	38.10%
Etoposide	10.71%	0.00%
Thalidomide	3.57%	0.00%
Lenalidomide	14.29%	2.38%
Melphalan	10.71%	0.00%
Panobinostat	3.57%	0.00%
Pomalidomide	7.14%	7.14%

Abbreviations: IsaPd, isatuximab, pomalidomide, low dose dexamethasone; Pd, pomalidomide, low dose dexamethasone.

Unit costs of subsequent treatments were based on values from the BNF and eMIT (Table 56). Estimated PAS discounts for daratumumab, pomalidomide and panobinostat were based on assumptions. As pomalidomide is the key treatment of comparison, the level of discount is tested in the sensitivity analysis. This may be considered conservative as there is more use of daratumumab monotherapy post progression on the pomalidomide arm.

Table 56: Costs for subsequent treatments

Drug	Cost per pack (£)	PAS discount (%)	Units per pack	mg per unit
Bendamustine	75.13‡		5	100
Bortezomib	762.38†		1	3.5
Carfilzomib	1,056.00†		1	60
Daratumumab	1,440.00†	[redacted]	1	400
Etoposide	11.50†		1	100
Thalidomide	6,336.00†		1	4
Lenalidomide	4,368.00†		21	25
Melphalan	45.38†		25	2
Pomalidomide	8,884.00†	[redacted]	21	4
Panobinostat	4,656.00†	[redacted]	6	20

Abbreviation: PAS, patient access scheme. †Source: BNF (118) ‡Source: eMIT (120)

Details on dosing for subsequent therapies are provided in Table 57. Average duration of treatment was estimated using data from a Kantar Health Study of treatments in RRMM in Western Europe (122). Duration of treatments not included in the Kantar Health Study were obtained from other published sources. In calculating the expected cost per course of therapy, TTD for subsequent therapies were assumed to follow an exponential distribution (i.e., constant hazard of discontinuation equal to the inverse of the mean TTD). Values for etoposide and bendamustine were collated from NHS regimen

information sheets (123, 124). For Pan and Bort, mean duration of treatment were from the manufacturer's submission to NICE for PanVd (122).

Table 57: Dosing and average duration of subsequent treatments

Drug	Cycle(s)	Daily dose	Days dosed per cycle	Weeks per cycle	Average duration (maximum cycles)
Bendamustine (41)	All	60 mg/m^2	2	4	6
Bortezomib (125)	1-8	1.3 mg/m^2	4	3	7
Carfilzomib (126)	1	20 mg/m^2	2	4	1
	1	27 mg/m^2	4	4	1
	2-12	27 mg/m^2	6	4	7
Daratumumab (127)	1+2	16 mg/kg	4	4	2
	3-6	16 mg/kg	2	4	3
	7+	16 mg/kg	1	4	5
Etoposide (41, 117)	All	40 mg/m^2	4	4	2
Thalidomide (128)	All	200 mg/day	42	1	4
Lenalidomide (129)	All	25 mg/day	21	4	9
Melphalan (41)	All	150 mg/m^2	4	6	4
Panobinostat (130)	1-8	20 mg/day	6	3	7
Pomalidomide (117)	All	4 mg/day	21	4	9

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

A summary of all the inputs used in the economic model is provided in Table 58. Base case results are reported in tables and figures. All outcomes are reported by health state. Costs are reported by category (medication, administration/dispensing, follow-up and monitoring, post-progression treatment) and health state. Utility values are reported by health state.

B.3.6.1 *Summary of base case analysis inputs*

Table 58: Summary of base case analysis inputs

Variable	Value	PSA distribution	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Patient characteristics at baseline				
Age, years	65.9	Empirical	Bootstrapped	Table 33
Percentage male, %	51.8	Empirical	Bootstrapped	
Weight, kg	73.3	Empirical	Bootstrapped	
Body surface area, m^2	1.8	Empirical	Bootstrapped	
Measures of efficacy				
Parametric distribution for PFS IsaPd and Pd	Lognormal (R)	Empirical	Bootstrapped	Table 36
Parametric distribution for PFS on treatment for IsaPd and Pd	Lognormal (R)	Empirical	Bootstrapped	Table 37
Parametric distribution for OS IsaPd and Pd	Exponential	Empirical	Bootstrapped	Table 35
Parametric distribution for TTD IsaPd and Pd	Exponential	Empirical	Bootstrapped	Table 38
Frequency of grade ≥3 adverse events, %				
Abdominal distention				Table 39
IsaPd	0	Empirical	Bootstrapped	
Pd	0	Empirical	Bootstrapped	
Abdominal pain				
IsaPd	0	Empirical	Bootstrapped	
Pd	0	Empirical	Bootstrapped	
Acute kidney injury				
IsaPd	4	Empirical	Bootstrapped	
Pd	5	Empirical	Bootstrapped	
Anaemia				
IsaPd	0	Empirical	Bootstrapped	
Pd	2	Empirical	Bootstrapped	
Asthenia				
IsaPd	2	Empirical	Bootstrapped	
Pd	3	Empirical	Bootstrapped	
Dehydration				
IsaPd	0	Empirical	Bootstrapped	

Pd	0	Empirical	Bootstrapped	
Diarrhoea				
IsaPd	4	Empirical	Bootstrapped	
Pd	0	Empirical	Bootstrapped	
Fatigue				
IsaPd	6	Empirical	Bootstrapped	
Pd	0	Empirical	Bootstrapped	
Febrile neutropenia				
IsaPd	14	Empirical	Bootstrapped	
Pd	5	Empirical	Bootstrapped	
Hypercalcaemia				
IsaPd	2	Empirical	Bootstrapped	
Pd	5	Empirical	Bootstrapped	
Hypokalaemia				
IsaPd	2	Empirical	Bootstrapped	
Pd	0	Empirical	Bootstrapped	
Hypophosphatemia				
IsaPd	0	Empirical	Bootstrapped	
Pd	0	Empirical	Bootstrapped	
Hypotension				
IsaPd	0	Empirical	Bootstrapped	
Pd	2	Empirical	Bootstrapped	
Lymphopenia				
IsaPd	0	Empirical	Bootstrapped	
Pd	0	Empirical	Bootstrapped	
Nausea				
IsaPd	0	Empirical	Bootstrapped	
Pd	0	Empirical	Bootstrapped	
Neutropenia				

IsaPd	43	Empirical	Bootstrapped	
Pd	29	Empirical	Bootstrapped	
Pneumonia				
IsaPd	18	Empirical	Bootstrapped	
Pd	16	Empirical	Bootstrapped	
Sepsis				
IsaPd	0	Empirical	Bootstrapped	
Pd	0	Empirical	Bootstrapped	
Septic Shock				
IsaPd	0	Empirical	Bootstrapped	
Pd	3	Empirical	Bootstrapped	
Syncope				
IsaPd	0	Empirical	Bootstrapped	
Pd	0	Empirical	Bootstrapped	
Thrombocytopenia				
IsaPd	6	Empirical	Bootstrapped	
Pd	10	Empirical	Bootstrapped	
Utility values by health states				Table 44
PFS on treatment (IsaPd)	0.731	Lognormal	0.695, 0.768	
PFS off treatment (IsaPd)	0.473	Lognormal	0.288, 0.658	
PFS on treatment (Pd)	0.717	Lognormal	0.677, 0.758	
PFS off treatment (Pd)	0.621	Lognormal	0.527, 0.714	
PPS on treatment	0.649	Lognormal	0.591, 0.707	
PPS off treatment	0.553	Lognormal	0.478, 0.629	
Terminal decrement	-0.204	Lognormal	-0.326, -0.083	
Duration of adverse events, days				Table 39
Abdominal distension	28			
Abdominal pain	28			
Acute kidney injury	28			
Anaemia	180			

Asthenia	28			
Dehydration	28			
Diarrhoea	28			
Fatigue	28			
Febrile neutropenia	28			
Flatulence	28			
Hypercalcaemia	28			
Hypokalaemia	0			
Hypophosphatemia	28			
Hypotension	0			
Lymphopenia	28			
Nausea	28			
Neutropenia	28			
Pneumonia	7			
Sepsis	28			
Septic shock	28			
Syncope	28			
Thrombocytopenia	28			
General population utility value regression coefficients				
Intercept	0.9508566	Lognormal		Table 45
Covariates				
Male vs female	0.0212126	Lognormal		
Age coefficient	-0.0002587	Lognormal		
Age-squared coefficient	-0.0000332	Lognormal		
Medication dosing				
IsaPd				Table 47
Isatuximab: Cycle 1				
Dose, mg/kg	10			
Days Dosed/Week	4			
Weeks/Cycle	4			
Maximum Cycles	1			
RDI, %	[redacted]	Beta	SE (0.224)	
Isatuximab: Cycle 2+				
Dose, mg/kg	10			
Days dosed/week	2			
Weeks/cycle	4			

Maximum cycles	-			
RDI, %	[redacted]	Beta	SE (0.224)	
Pomalidomide: all cycles				
Dose, mg/day	4			
Days dosed/week	21			
Weeks/cycle	4			
Maximum cycles	-			
RDI, %	[redacted]	Beta	SE (0.200)	
Dexamethasone: all cycles				
Dose, mg/day	40			
Days dosed/week	4			
Weeks/cycle	4			
Maximum cycles	-			
RDI, %	[redacted]	Beta	SE (0.200)	
Pd				
Pomalidomide: all cycles				
Dose, mg/day	4			
Days dosed/week	21			
Weeks/cycle	4			
Maximum cycles	-			
RDI, %	86.63	Beta	SE (0.217)	
Dexamethasone: all cycles				
Dose, mg/day	40			
Days dosed/week	4			
Weeks/cycle	4			
Maximum cycles	-			
RDI, %	86.63	Beta	SE (0.217)	
Medication costs				
Isatuximab				Table 48
Cost/pack, £	[redacted]			
PAS discount, %	[redacted]			
Units/pack	1			
mg/unit	100			
Pomalidomide				
Cost/pack, £	8,884.00			
Assumed PAS discount, %	[redacted]			

Units/pack	21			
mg/unit	4			
Dexamethasone, oral				
Cost/pack, £	200.00			
PAS discount, %	0			
Units/pack	10			
mg/unit	40			
Panobinostat				
Cost/pack, £	4,656.00			
Assumed PAS discount, %	[redacted]			
Units/pack	6			
mg/unit	20			
Bortezomib				
Cost/pack, £	762.38			
PAS discount, %	0			
Units/pack	1			
mg/unit	3.5			
Dexamethasone, IV				
Cost/pack, £	32.50			
PAS discount, %	0			
Units/pack	5			
mg/unit	2			
Administration Costs, £				
Oral, first dose	132	Lognormal (SD:Mean 25%)		Table 49
Oral, subsequent dose(s)	0			
Injection, first dose	174	Lognormal (SD:Mean 25%)		
Injection, subsequent dose(s)	174	Lognormal (SD:Mean 25%)		
IV, first dose	252	Lognormal (SD:Mean 25%)		
IV, subsequent dose(s)	233	Lognormal (SD:Mean 25%)		
Cost of Premedication, £				
Corticosteroid (methylprednisolone IV)	4.75			Table 50
Antipyretic (acetaminophen)	0.74			
Antihistamine (cetirizine hydrochloride)	0.16			
Acetylsalicylic acid	0.47			
Cost of Concomitant Treatments				
GCSF				Table 51

Unit cost, £	52.70			
Mean number per patient	1			
Percent receiving by treatment				
IsaPd	43			
Pd	43			
RBC transfusions				
Unit cost, £	121.85			
Mean number per patient	3			
Percent receiving by treatment				
IsaPd	49			
Pd	49			
Platelet Transfusions				
Unit cost, £	196.96			
Mean number per patient	4.79			
Percent receiving by treatment				
IsaPd	20			
Pd	20			
Costs of treating adverse events, £				
Abdominal distension	2,362.11	Lognormal (SD:Mean 25%)		Table 54
Abdominal pain	2,362.11	Lognormal (SD:Mean 25%)		
Acute kidney injury	1,447.87	Lognormal (SD:Mean 25%)		
Anaemia	691.09	Lognormal (SD:Mean 25%)		
Asthenia	727.55	Lognormal (SD:Mean 25%)		
Dehydration	0.00	Lognormal (SD:Mean 25%)		
Diarrhoea	546.61	Lognormal (SD:Mean 25%)		
Fatigue	727.55	Lognormal (SD:Mean 25%)		
Febrile neutropenia	7,230.00	Lognormal (SD:Mean 25%)		
Hypercalcaemia	4,098.18	Lognormal (SD:Mean 25%)		
Hypokalaemia	435.50	Lognormal (SD:Mean 25%)		
Hypophosphatemia	435.50	Lognormal (SD:Mean 25%)		
Hypotension	1,077.36	Lognormal (SD:Mean 25%)		
Lymphopenia	1,077.36	Lognormal (SD:Mean 25%)		
Nausea	727.55	Lognormal (SD:Mean 25%)		

Neutropenia	1,077.36	Lognormal (SD:Mean 25%)		
Pneumonia	1,784.00	Lognormal (SD:Mean 25%)		
Sepsis	3,997.10	Lognormal (SD:Mean 25%)		
Septic Shock	3,997.10	Lognormal (SD:Mean 25%)		
Syncope	0	Lognormal (SD:Mean 25%)		
Thrombocytopenia	640.09	Lognormal (SD:Mean 25%)		
Costs of follow-up, £				
Physician visit	160.00	Lognormal (SD:Mean 25%)		Table 52
Complete blood count test	3.00	Lognormal (SD:Mean 25%)		
Biochemistry	1.00	Lognormal (SD:Mean 25%)		
On-therapy PFS number of physician visits per month	1			Section B.3.5.6.1
On-therapy PFS number of blood counts per month	1			
On-therapy PFS number of biochemistry visits per month	1			
Off-therapy PFS number of physician visits per month	1			
Off-therapy PFS number of blood counts per month	1			
Off-therapy PFS number of biochemistry visits per month	1			
On-therapy post-progression number of physician visits per month	1			
On-therapy post-progression number of blood counts per month	1			
On-therapy post-progression number of biochemistry visits per month	1			
Off-therapy post-progression number of physician visits per month	1			
Off-therapy post-progression number of blood counts per month	1			
Off-therapy post-progression number of biochemistry visits per month	1			
Proportion of patients receiving subsequent treatments, %				
Bendamustine				Table 55

IsaPd	10.71	Empirical	Bootstrapped	
Pd	11.90	Empirical	Bootstrapped	
Bortezomib				
IsaPd	25.00	Empirical	Bootstrapped	
Pd	16.67	Empirical	Bootstrapped	
Carfilzomib				
IsaPd	17.86	Empirical	Bootstrapped	
Pd	21.43	Empirical	Bootstrapped	
Daratumumab				
IsaPd	7.14	Empirical	Bootstrapped	
Pd	38.10	Empirical	Bootstrapped	
Etoposide				
IsaPd	10.71	Empirical	Bootstrapped	
Pd	0	Empirical	Bootstrapped	
Thalidomide				
IsaPd	3.57	Empirical	Bootstrapped	
Pd	0	Empirical	Bootstrapped	
Lenalidomide				
IsaPd	14.29	Empirical	Bootstrapped	
Pd	2.38	Empirical	Bootstrapped	
Melphalan				
IsaPd	10.71	Empirical	Bootstrapped	
Pd	0	Empirical	Bootstrapped	
Panobinostat				
IsaPd	3.57	Empirical	Bootstrapped	
Pd	0	Empirical	Bootstrapped	
Pomalidomide				
IsaPd	7.14	Empirical	Bootstrapped	
Pd	7.14	Empirical	Bootstrapped	
Costs of subsequent treatments				
Bendamustine				Table 56
Cost/pack, £	75.13			
PAS discount, %	-			
Units/pack	5			
mg/unit	100			
Bortezomib				

Cost/pack, £	762.38			
PAS discount, %	-			
Units/pack	1			
mg/unit	3.5			
Carfilzomib				
Cost/pack, £	1,056.00			
PAS discount, %	-			
Units/pack	1			
mg/unit	60			
Daratumumab				
Cost/pack, £	1,440.00			
Assumed PAS discount, %	[redacted]			
Units/pack	1			
mg/unit	400			
Etoposide				
Cost/pack, £	11.50			
PAS discount, %	-			
Units/pack	1			
mg/unit	100			
Thalidomide				
Cost/pack, £	298.48			
PAS discount, %	-			
Units/pack	28			
mg/unit	50			
Lenalidomide				
Cost/pack, £	4,368.00			
PAS discount, %	-			
Units/pack	21			
mg/unit	25			
Melphalan				
Cost/pack, £	45.38			
PAS discount, %	-			
Units/pack	25			
mg/unit	2			
Pomalidomide				
Cost/pack, £	8,884.00			

Assumed PAS discount, %	[redacted]			
Units/pack	21			
mg/unit	4			
Panobinostat				
Cost/pack, £	4,656.00			
Assumed PAS discount, %	[redacted]			
Units/pack	6			
mg/unit	20			
Medication dosing for subsequent treatments				
Bendamustine				Table 57
Daily dose, mg/m^2	60			
Days dosed/cycle	2			
Weeks/cycle	4			
Average duration, number of cycles	6			
Bortezomib				
Daily dose, mg/m^2	1.3			
Days dosed/cycle	4			
Weeks/cycle	3			
Average duration, number of cycles	7			
Carfilzomib – Cycle 1				
Daily dose, mg/m^2	20			
Days dosed/cycle	2			
Weeks/cycle	4			
Average duration, number of cycles	1			
Carfilzomib – Cycle 1, Initial Dose				
Daily dose, mg/m^2	20			
Days dosed/cycle	2			
Weeks/cycle	4			
Average duration, number of cycles	1			
Carfilzomib – Cycle 1, Subsequent Doses				
Daily dose, mg/m^2	27			
Days dosed/cycle	4			
Weeks/cycle	4			
Average duration, number of cycles	1			
Carfilzomib – Cycles 2+				
Daily dose, mg/m^2	27			

Days dosed/cycle	6			
Weeks/cycle	4			
Average duration, number of cycles	7			
Daratumumab – Cycles 1-2				
Daily dose, mg/kg	16			
Days dosed/cycle	4			
Weeks/cycle	4			
Average duration, number of cycles	2			
Daratumumab – Cycles 3-6				
Daily dose, mg/kg	16			
Days dosed/cycle	2			
Weeks/cycle	4			
Average duration, number of cycles	3			
Daratumumab – Cycles 7+				
Daily dose, mg/kg	16			
Days dosed/cycle	1			
Weeks/cycle	4			
Average duration, number of cycles	5			
Etoposide				
Daily dose, mg/m^2	40			
Days dosed/cycle	4			
Weeks/cycle	4			
Average duration, number of cycles	2			
Thalidomide				
Daily dose, mg/day	200			
Days dosed/cycle	42			
Weeks/cycle	6			
Average duration, number of cycles	4			
Lenalidomide				
Daily dose, mg/day	25			
Days dosed/cycle	21			
Weeks/cycle	4			
Average duration, number of cycles	9			
Melphalan				
Daily dose, mg/m^2	150			
Days dosed/cycle	4			

Weeks/cycle	6			
Average duration, number of cycles	4			
Panobinostat				
Daily dose, mg/day	20			
Days dosed/cycle	6			
Weeks/cycle	3			
Average duration, number of cycles	7			
Pomalidomide				
Daily dose, mg/day	4			
Days dosed/cycle	21			
Weeks/cycle	4			
Average duration, number of cycles	9			
% of progressing patients on therapy post-progression				
IsaPd,	73.9	Empirical	Bootstrapped	Table 53
Pd	72.7	Empirical	Bootstrapped	
Mean duration of post-progression treatment, months				
IsaPd	2.29	Empirical	Bootstrapped	Table 53
Pd	1.54	Empirical	Bootstrapped	
Terminal care costs, £	894.15	Lognormal (SD:Mean 25%)		Section B.3.5.6.2

B.3.6.2 *Assumptions*

The assumptions utilized in the economic analysis are described below. The approach to modelling has been designed to make the best use of the available data to inform the decision problem, in line with the NICE reference case and guidance on methods of appraisal (Table 59). In the absence of data, assumptions are implemented to minimise potential bias in the analysis.

Table 59: Model assumptions

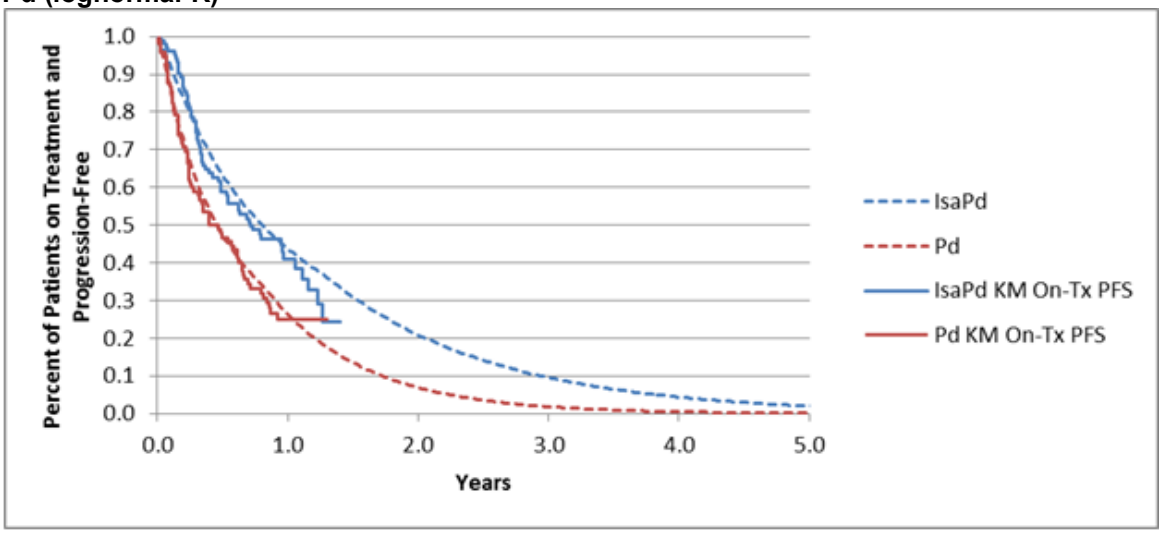
Area	Assumption	Justification
Time horizon	15 years	The time horizon was considered long enough to capture the long-term clinical and economic impacts of RRMM, an incurable disease requiring treatment until end of life. Given the median age of 65.9 years for the ICARIA-MM trial population, 15 years is a fair approximation of a lifetime time horizon
Model cycle length	1 week	Sufficiently short to accurately capture clinical outcomes and differences in treatment administrations, with no need for a health cycle correction
Discount	3.5%	Per the Guidelines for Economic Evaluation of HTAs in the UK
Modelling approach	PSM	A PSM closely models PFS and OS trial data without and is commonly used in oncology models as reported in the NICE DSU technical support document (80) and in prior evaluations of treatments for RRMM
Population	Patients who have received 3 prior lines of treatment including lenalidomide	Aligned to the anticipated place in therapy.
Extrapolation	TTD, PFS on treatment, PFS, and OS curves were extrapolated by fitting parametric distributions to the KM curves. Curve selections were based on best statistical fit and clinical face validity of predictions	Per NICE DSU guidance. Because the ICARIA trial duration was insufficiently long to capture the full long-term benefits of IsaPd and Pd, survival had to be extrapolated beyond the end of trial follow-up
Treatment duration	Follows TTD distribution in ICARIA-MM	TTD distributions were estimated based on the ICARIA-MM trial data.
Subsequent treatments	Top 10 most frequently prescribed medications included as post-study therapies. The dosing of these therapies was taken from their respective prescribing information, and the average duration of	The ICARIA-MM trial data included use of medications patients received after discontinuation with IsaPd and Pd. The frequencies were not reported by regimen; therefore, some patients may have received more than one medication, and some received no post-study treatment. As there were very many different medications administered after

	therapy was based on data from Kantar Health for Western Europe (122)	completion of ICARIA-MM, only the top 10 most frequent medications were included in the model for conciseness, as these are most likely to reflect the post-study therapies available in a real-world setting. Duration of these treatments was not captured in ICARIA-MM, and therefore, Kantar Health data was chosen as the best available estimate for typical clinical practice in the UK. Utility data as recorded in ICARIA-MM for subsequent treatments have also been included.
Adverse event costs	The model includes AEs for which Grade 3 or higher events were reported in at least 5% of the patients in any of the treatment arms of ICARIA-MM or for the relevant pivotal trials of the key comparators	This inclusion rule captures important AEs and is consistent with procedures utilised in a number of other RRMM submissions
PAS discounts	[redacted] discount for Pom [redacted] discount for Panobinostat and daratumumab monotherapy	As Sanofi cannot know what the accepted discount rates for the IsaPd comparator therapies in the UK are, therefore, the PAS discount rates for the comparators were assumed. Pomalidomide discount has been tested in SA as it the key comparator of this submission.
Follow-up costs	Follow-up costs were assumed to be the same for all treatments	The frequencies and types of follow-up and monitoring costs used in the model were based on clinical expertise in the UK, with clinicians believing that resource use would not vary by treatment
General population mortality and utilities	General population mortality and utilities applied as floor and ceiling, respectively	It was assumed that survival and utilities among all treatments would not exceed that of the general population

B.3.7 *Base-case results*

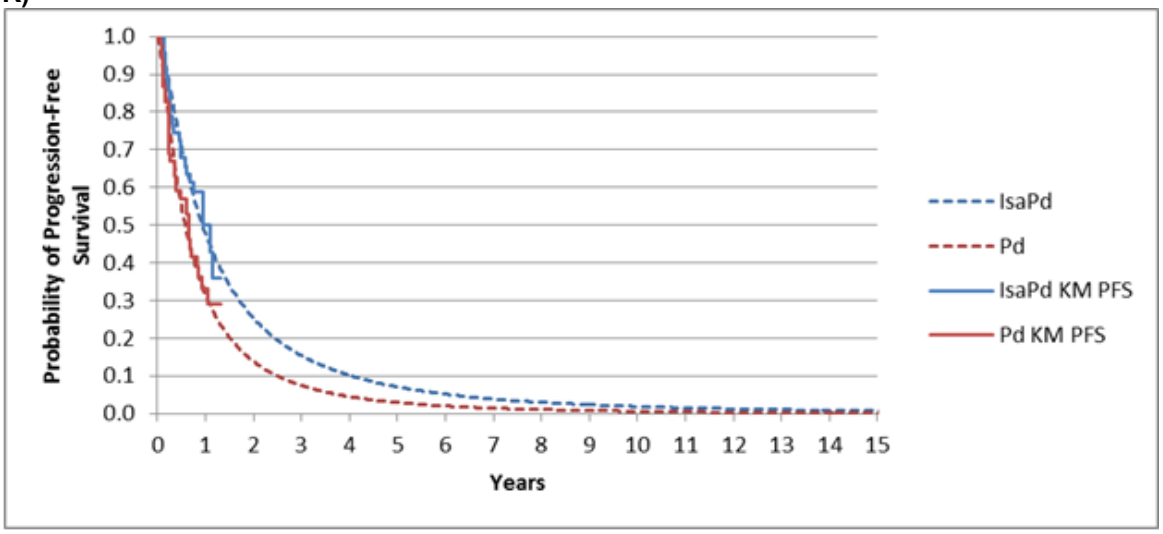
KM curves and model projections for PFS on treatment, PFS, TTD and OS at 5 years are shown in Figure 37 to Figure 40. As noted above, for the base case, all estimates from ICARIA-MM were based on results for the subgroup of patients who had received 3 prior lines of therapy (4L patients).

Figure 37: Model Projection of PFS on treatment and KM Estimates of PFS for IsaPd and Pd (lognormal-R)



Abbreviations: IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; KM, Kaplan-Meyer; Pd, pomalidomide, low-dose dexamethasone; PFS, progression free survival; Tx, treatment.

Figure 38: Model Projection of PFS and KM Estimates of PFS for IsaPd and Pd (lognormal-R)



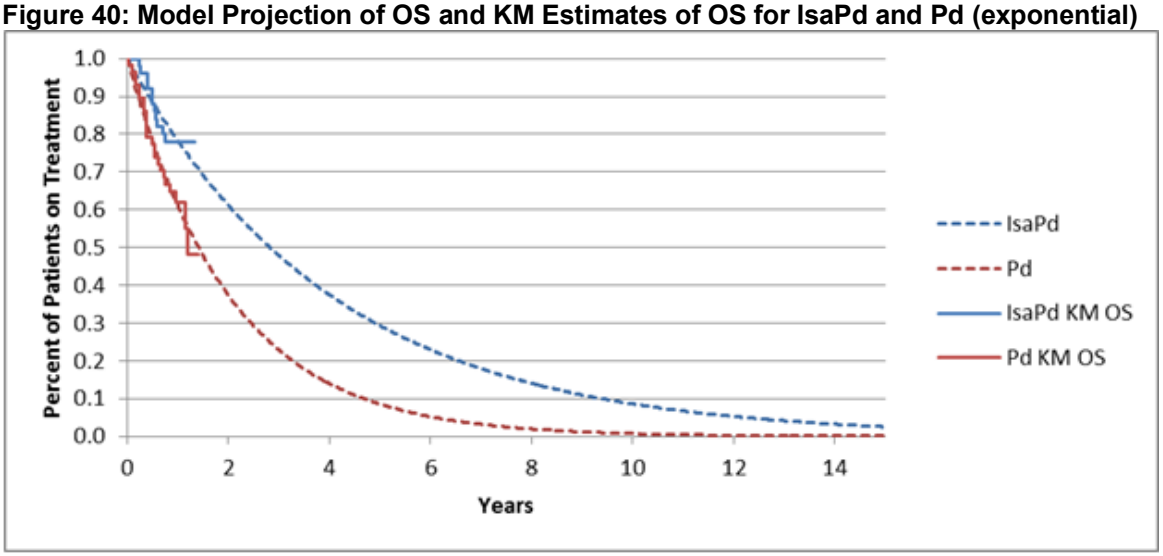
_Abbreviations: IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; KM, Kaplan-Meyer; Pd, pomalidomide, low-dose dexamethasone; PFS, progression free survival; Tx, treatment.

Figure 39: KM and model projection of TTD for IsaPd and Pd (exponential)

[redacted]

[redacted]

Figure 40: Model Projection of OS and KM Estimates of OS for IsaPd and Pd (exponential)



_Abbreviations: IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; KM, Kaplan-Meyer; OS, overall survival; Pd, pomalidomide, low-dose dexamethasone; Tx, treatment.

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

Table 60 displays base case cost-effectiveness results in terms of pairwise comparisons between IsaPd and Pd. Results are presented applying confidential patient access scheme (PAS) discounts of [redacted] to the list price for isatuximab and an assumed discount of [redacted] to the list price for pomalidomide.

IsaPd is estimated to offer a high per-patient incremental health benefit, providing nearly twice as many life years (LYs) and time-preference discounted QALYs than pomalidomide ([redacted] LYs and [redacted] QALYs for IsaPd vs [redacted] LYs and [redacted] QALYs for Pd). Despite the significant clinical and QoL benefit, the estimated incremental cost-effectiveness ratio (ICER) for IsaPd vs pomalidomide is £125,948 per QALY gained. This

is largely because Pd contributes nearly [redacted] of the total drug cost for IsaPd even with an assumed PAS.

Estimated disaggregated results are presented in Appendix K.

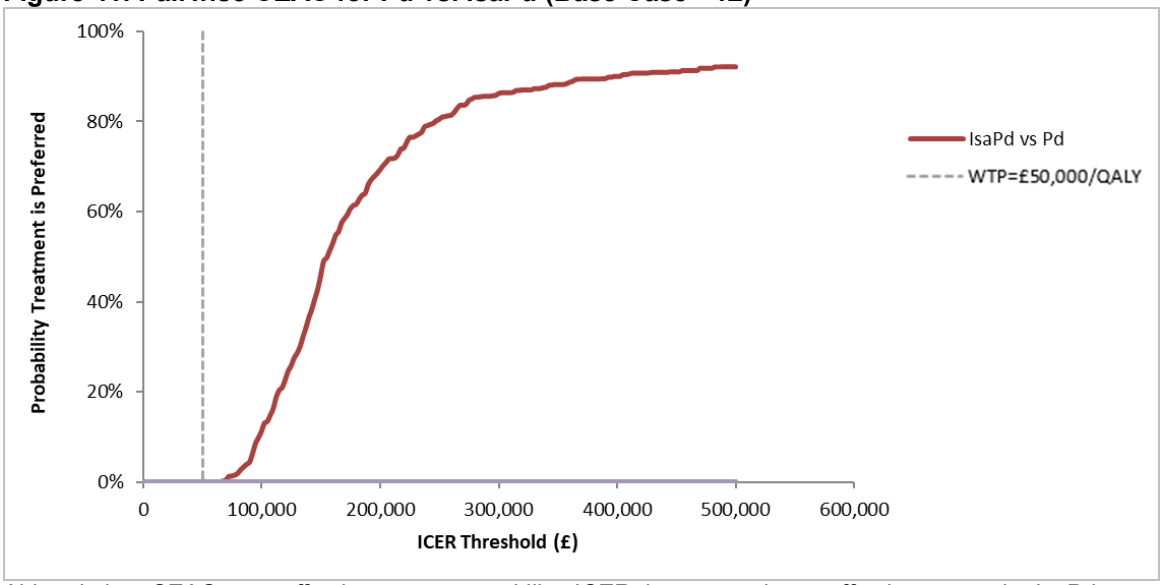
Table 60: Base-case results (deterministic)

Outcome	IsaPd	Pd
Totals, discounted		
Costs (£)	[redacted]	[redacted]
LYs	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
Difference IsaPd vs. Pd		
Costs (£)		120,594
LYs		1.649
QALYs		0.957
ICER (IsaPd) vs comparator		
Cost (£) per life-year saved		73,140
Cost (£) per QALY saved		125,948

Abbreviations: IsaPd, isatuximab+ pomalidomide+ dexamethasone; LY, life year; Pd, pomalidomide+ dexamethasone; QALY, quality-adjusted life year.

The pairwise CEAC for Pd vs IsaPd is shown in Figure 41.

Figure 41: Pairwise CEAC for Pd vs. IsaPd (Base Case - 4L)



Abbreviation: CEAC, cost-effectiveness acceptability; ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; Pd, pomalidomide, low-dose dexamethasone; QALY, quality-adjusted life year; WTP, willingness-to-pay.

B.3.7.2 *Clinical outcomes from the model*

Model predictions vs trial outcomes for 4L patients with RRMM are shown in Table 61.

Table 61: Percentiles of PFS, TTD, and OS for IsaPd and Pd from model vs ICARIA-MM trial

Variable	Model		ICARIA-MM	
	IsaPd	Pd	IsaPd	Pd
Percentiles of TTD (months)				
25%	[redacted]	[redacted]	[redacted]	[redacted]
50%	[redacted]	[redacted]	[redacted]	[redacted]
75%	[redacted]	[redacted]	N/A	N/A
Percentiles of PFS (months)				
25%	5.2	3.1	4.1	2.9
50%	11.2	7.0	13.3	7.8
75%	24.3	15.1	NR	NR
Percentiles of OS (months)				
25%	14.2	7.0	NR	6.6
50%	33.9	16.9	NR	14.4
75%	67.8	33.7	NR	NR
Landmark TTD by months				
6	[redacted]%	[redacted]%	[redacted]%	[redacted]%
12	[redacted]%	[redacted]%	[redacted]%	[redacted]%
24	[redacted]%	[redacted]%	N/A	N/A
36	[redacted]%	[redacted]%	N/A	N/A
48	[redacted]%	[redacted]%	N/A	NA
60	[redacted]%	[redacted]%	N/A	NA
Landmark PFS by months				
6	70.4%	54.5%	67.9%	57.0%
12	47.5%	31.4%	50.1%	33.1%
24	25.3%	13.8%	NA	NA
36	15.4%	7.5%	NA	NA
48	10.2%	4.5%	NA	NA
60	7.1%	2.9%	NA	NA
Landmark On-Tx PFS by months				
6	62.9%	46.9%	63.3%	52.0%
12	43.5%	26.1%	45.1%	28.2%
24	20.9%	6.9%	N/A	N/A
36	9.6%	1.8%	N/A	N/A
48	4.4%	0.5%	N/A	N/A
60	2.0%	0.1%	N/A	N/A
Landmark OS by months				
6	88.3%	77.9%	88.0%	77.3%
12	78.1%	60.9%	78.0%	61.9%
24	61.2%	37.3%	NR	NR

Variable	Model		ICARIA-MM	
	IsaPd	Pd	IsaPd	Pd
36	47.9%	22.9%	NR	NR
48	37.5%	14.0%	NR	NR
60	29.3%	8.6%	NR	NR

Abbreviations: IsaPd, isatuximab+ pomalidomide+ dexamethasone; OS, overall survival; Pd, pomalidomide+ dexamethasone; PFS, progression-free survival; TTD, time to discontinuation.

B.3.8 *Sensitivity analyses*

B.3.8.1 *Probabilistic sensitivity analysis (PSA)*

In the model PSAs were generated by simultaneously sampling from estimated probability distributions of model parameters. The distributions selected are shown in Table 58. For parameters that are correlated, the model will permit inputting of covariance matrices (using the Cholesky decomposition of the matrix to sample from the multivariate distribution). Alternatively, the model may utilise joint bootstrap distributions for these parameters derived from bootstrap samples of data from the ICARIA-MM trial. For each simulation, expected costs and QALYs are calculated for each comparator, along with the differences between comparators in expected costs and QALYs. Descriptive statistics are generated based on the simulated values for costs, QALYs, incremental costs, and incremental QALYs, and NMB. Ninety-five percent credible intervals are calculated for these outcomes based on the 2.5 and 97.5 percentiles of the simulations. For each comparison, simulation results are plotted on the cost-effectiveness plane. Cost-effectiveness acceptability curves (CEACs) are constructed for each comparator.

Mean results of the probabilistic sensitivity analyses of pairwise cost-effectiveness for IsaPd vs its comparators are provided in Table 62.

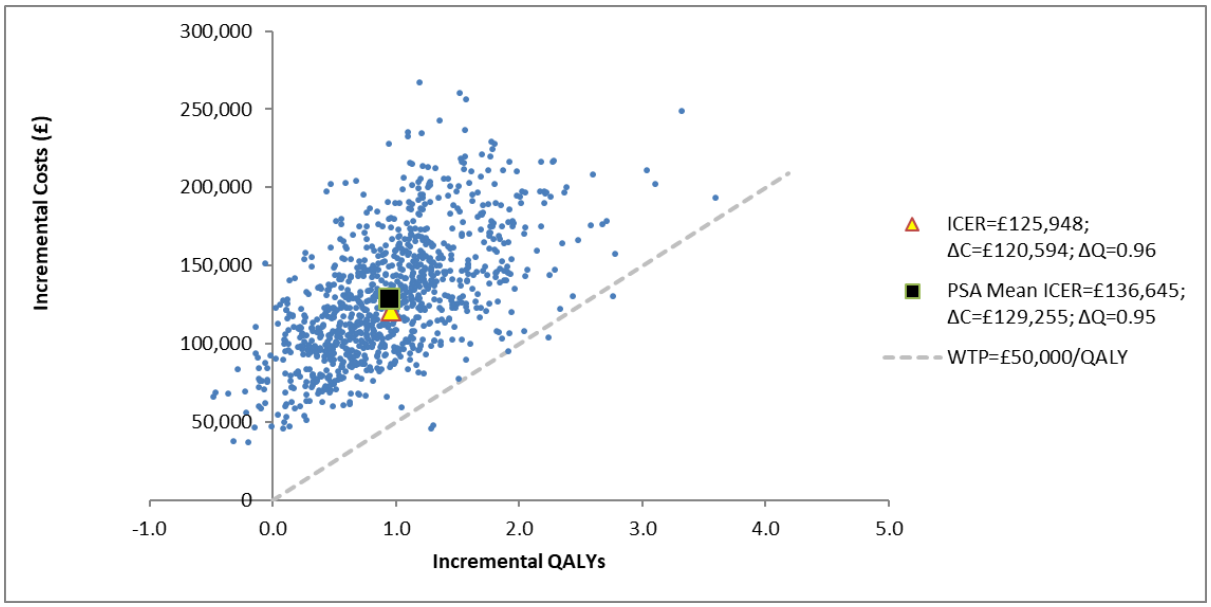
Table 62: Base-case results (probabilistic)

Outcome	IsaPd	Pd
Totals, discounted		
Costs (£)	[redacted]	[redacted]
LYs	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
Difference IsaPd vs. Pd		
Costs (£)		129,255
LYs		1.63
QALYs		0.95
ICER (IsaPd) vs comparator		
Cost (£) per life-year saved		79,400
Cost (£) per QALY saved		136,645

Abbreviations: IsaPd, isatuximab+ pomalidomide+ dexamethasone; LY, life year; Pd, pomalidomide+ dexamethasone; QALY, quality-adjusted life year.

A scatter plot of the joint distribution of incremental costs and incremental QALYs from the PSA is provided in Figure 42. Most of the simulation results are in the northeast quadrant and above the WTP threshold, with a small proportion in the northwest quadrant. As the entirety of the observations remain above the WTP threshold, there are no observations in which IsaPd is determined to be cost-effective at the given WTP.

Figure 42: Scatter plot of simulations on cost-effectiveness plane



Abbreviations: CEAC, cost-effectiveness acceptability curve; ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab+ pomalidomide+ dexamethasone; Pd, pomalidomide+ dexamethasone; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

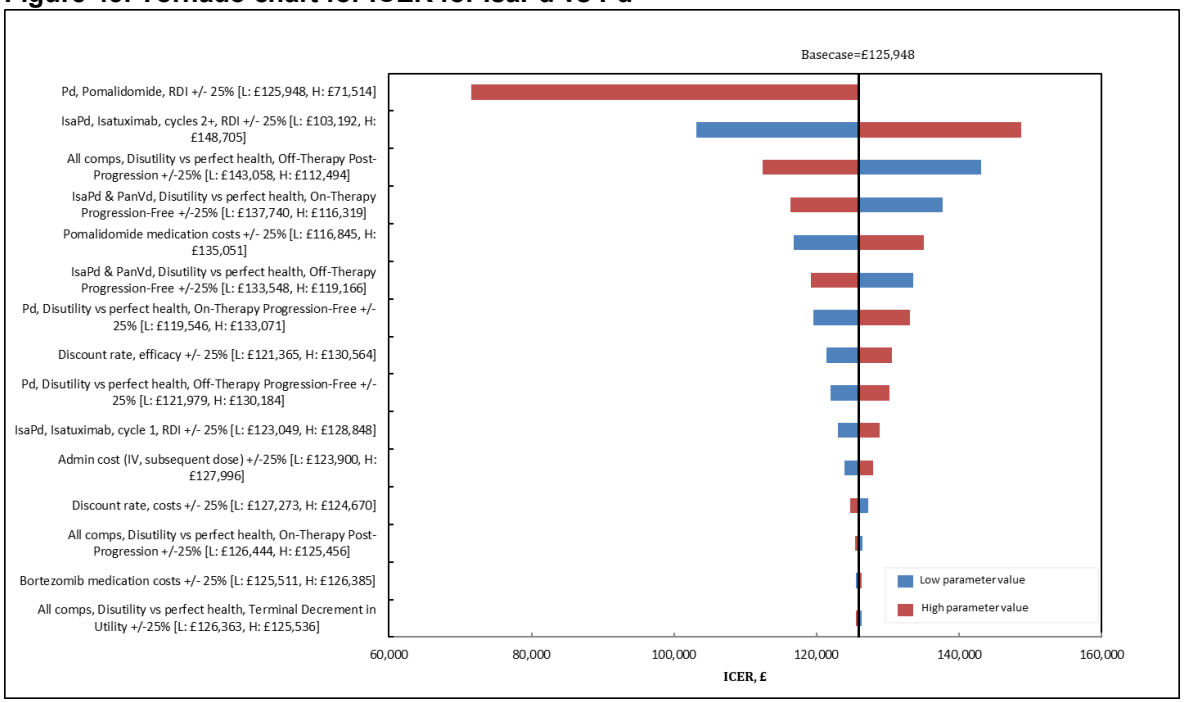
B.3.8.2 *Deterministic sensitivity analysis*

Deterministic sensitivity analyses (DSAs) have been conducted to explore the impact of changing assumptions concerning key model parameter values on the plausible incremental cost-effectiveness ratio. Tornado diagrams, in which a numerical variable is varied over a specified range in order to measure its impact on cost-effectiveness, were generated. Parameters included in tornado diagrams were varied by their 95% CIs or by ±25% in the absence of data on CIs in order to assess the relative impact of these parameters on the cost-effectiveness estimates.

B.3.8.2.1 Results

Results of the deterministic sensitivity analyses on the ICER for IsaPd vs comparators of interest are shown in Figure 43. For the comparison of IsaPd vs Pd, the ICER is sensitive to the IsaPd off treatment post-progression disutility value and the Pd RDI.

Figure 43: Tornado chart for ICER for IsaPd vs Pd



Abbreviations: H, high; ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab+ pomalidomide+ dexamethasone; L, low; Pd, pomalidomide+ dexamethasone.

B.3.8.3 *Scenario analysis*

Results of scenario analyses are shown in Table 63. Compared with the base case scenario, the ICER per QALY gained for IsaPd vs Pd ranges from £60,090 to £247,283.

Table 63: Summary of scenario analyses for IsaPd vs Pd

Scenario name	Base case	Scenario description	vs Pd (£)
Base case ([redacted] discount)	In the base case, a XXX PAS discount for Isa is applied		125,948
No medication wastage	All medication is dosed by vials or tablets (where applicable), therefore, patients incur the cost of unused medication	All medication is dosed by mg, allowing for the possibility of using a fraction of a vial, therefore, resulting in no medication wastage	109,281
EQ-5D-5L utilities	EQ-5D-3L utility values were used, based on the NICE recommendation	EQ-5D-5L utility values were considered	109,251
No PAS discount for Pom	A XXX PAS discount was assumed for the medication cost of Pom	No PAS discount was applied to the cost of Pom	150,223
		XXX PAS discount was applied to the cost of Pom	144,154
		XXX PAS discount was applied to the cost of Pom	138,085
		XXX PAS discount was applied to the cost of Pom	132,017
		XXX PAS discount was applied to the cost of Pom	119,880
Using KOL preferred curves for PFS	Lognormal (R) based on visual fit, statistical fit and clinical plausibility	RCS Weibull (R)	126,829
		Weibull (R)	122,124
		Exponential	122,292
		Gompertz (R)	121,916
% receiving subsequent therapy and duration of subsequent therapy based on KOL feedback	The percent of patients receiving Subsequent therapies were taken from the ICARIA-MM trial for the IsaPd and Pd arms. Given the variety in medications administered, only the top 10 most frequently used medications were considered. Also, in the base case, the duration of treatment with the post-study anti-cancer therapies was based on data from Kantar Health for Western Europe (122) and literature, if not available in Kantar Health	In this scenario, feedback from three clinicians was used to inform the percentage of patients receiving subsequent therapies and the duration of said therapies in real-world UK clinical practice (79)	132,334
Favourable distributions for IsaPd	The distributions for TTD, on-treatment PFS, PFS, and OS with the best BIC and visual fit to the ICARIA-MM KM data were	In this scenario, the next best fitting distributions that were more favourable for IsaPd than in the base case were selected, and are as follows:	86,930

	selected for the base case	• TTD: Weibull (U) • On-Tx PFS: RCS lognormal (R) • PFS: RCS Weibull (R) • OS: RCS Weibull (R)	
Unfavourable distributions for IsaPd		In this scenario, the next best fitting distributions that were less favourable for IsaPd than in the base case were selected, and are as follows: • TTD: Log-logistic (R) • On-treatment PFS: Log-logistic (R) • PFS: RCS Lognormal (R)• OS: Lognormal (R)	201,624
Other costs from Dara NICE submission	The frequency of follow-up and monitoring visits were based on feedback from UK clinicians	In this scenario, the frequency of these follow-up visits was taken from the Dara NICE submission (14)	122,917
Treatment discontinued upon progression, lognormal (R) (best BIC)	TTD distributions from ICARIA-MM were used to determine duration of treatment for each treatment arm	In this scenario, on-treatment PFS was used as a proxy for TTD and the percent of patients receiving treatment after progression was set to 0% • In the ICARIA-MM trial, assessment of progression was determined by a blood sample, and it took on average 2 months after the blood sample was taken to determine progression, and therefore, patients stayed on treatment an average of 2 months after progression, although they should stop treatment upon progression, according to the ICARIA-MM trial protocol • The restricted lognormal distribution was selected for on-treatment PFS for this scenario because it has the best BIC statistical fit	164,742
Treatment discontinued upon progression, exponential		In this scenario, on-treatment PFS was used as a proxy for TTD and the percent of patients receiving treatment after progression was set to 0% • The exponential distribution was selected for on-treatment PFS this scenario, to be consistent with the TTD distribution used in the base case	116,530
5-year time horizon	In the base case, a 15-year time horizon was selected as a close approximation of the population's expected lifetime (given the average starting age in ICARIA-MM of	In these scenario, different time horizons were considered	201,091
10-year time horizon			137,769
20-year time horizon			123,244

	65 years)		
1.5% effectiveness discount rate	In the base case, a discount rate of 3.5% was applied to both costs and effectiveness, as recommended by NICE	In this scenario, a lower discount rate of 1.5% for effectiveness was tested. Costs were discounted at 3.5%	115,524
1.5% discount rate		In this scenario, a lower discount rate of 1.5% for both was tested	118,370
Isa dosing based on ICARIA-MM weight distribution	Mean weight was used for computing Isa dosing	Based on separate calculations examining the cost difference when weight distribution vs mean weight was used in Isa costing where it was found that using weight distribution results in a 30% overall cost of Isa, for this scenario, a discount of XXXX was applied to the Isa cost.	123,222
All unfavourable inputs	With wastage (vial costing), EQ-5D-3L, distributions based on statistical fit, visual fit and clinical plausibility	Combination of all the inputs above that result in increase of ICER, including use of no PAS discount for Pom, % receiving subsequent therapy and duration of subsequent therapy based on KOL feedback, and unfavourable distributions for IsaPd	247,283
Optimising all Favourable inputs	With wastage (vial costing), EQ-5D-3L, distributions based on statistical fit, visual fit and clinical plausibility.	Combination of all the inputs above that result in decrease of ICER, including use of no medication wastage, EQ-5D-5L utilities, favourable distributions for IsaPd, other costs from NICE submission, and Isa dosing based on weight distribution	60,090

Abbreviations: BIC, Bayesian information criterion; Isa, isatuximab; IsaPd, isatuximab+ pomalidomide+ dexamethasone; KM, Kaplan Meier; PAS, patient access scheme; Pd, pomalidomide+ dexamethasone; PFS, progression-free survival; Pom, pomalidomide; RCS, restricted cubic spline; TTD, time to discontinuation.

B.3.8.4 *Summary of sensitivity analyses results*

While there is uncertainty around the cost-effectiveness of IsaPd in 4L patients, care has been taken to inform uncertain assumptions with the best data available, implementing parametric modelling of clinical outcomes according to NICE DSU TSD 14 (131). Assumptions have been validated by clinical experts.

Sensitivity and scenario analysis results showed results to move in expected directions around input parameters such as time horizon and discount rates. Survival assumptions, however, and those that affect expected treatment acquisition cost, are clearly important drivers of cost-effectiveness. The extrapolations of PFS and OS are subject to uncertainty due to the immaturity on the data set. This uncertainty will be reduced when the final survival analysis becomes available and so we strongly believe that isatuximab should be considered for routing into the CDF.

B.3.9 *Validation*

B.3.9.1 *Validation of de novo cost-effectiveness analysis*

The model has been validated by an independent group of analysts ("validation team"). The following validation checks were performed:

1. Pressure testing on extreme value/edge cases
2. Checking results of sensitivity analyses against priors
3. Checking results of PSA against point estimates
4. Identification of #REF, #NUM, and #NA errors;
5. Identify unused calculations;
6. Identify unused named ranges;
7. Identify hard-coded values within formulas;
8. Identify overly complex/difficult to parse formulas;
9. Check that there are no links to other workbooks or external files;
10. Check index/lookup functions for offset errors;
11. Check that discounting is applied appropriately;
12. Check that half-cycle correction is applied appropriately (if applicable);
13. Check that model restores appropriately if simulation is terminated prematurely;
14. Test model control objects (buttons etc.) for functionality;
15. Check that "restore defaults" or similar functionality works correctly;
16. Check the model inputs against the study report (if available);
17. Check that all input values are appropriately referenced;
18. Check model formatting (e.g., inputs one colour fill, results a different colour fill);
19. Check that x- and y-axis ranges on model charts change as results change;
20. Check that model is free of spelling and grammar errors; and,
21. Test the model on a (limited) set of different computers.

An additional validation was conducted by an external agency contracted by Sanofi. Any issues identified were addressed in the final model. The internal Sanofi team also checked the model inputs and engine.

B.3.10 *Interpretation and conclusions of economic evidence*

Despite the availability of treatments in the 4L setting the median overall survival, in these heavily pre-treated patients, is less than two years. Evidence from ICARIA-MM suggest that survival prospects for these patients can be improved with IsaPd since it is the first triplet treatment to have demonstrated a PFS longer than 12 months in the 4L population; median PFS was prolonged in the IsaPd arm (13.31 months [95% CI; 7.425, NC) in comparison with the Pd arm (7.82 months [95% CI; 4.468, 11.072]). The stratified hazard ratio was 0.598 (95% CI; 0.348, 1.030) representing a 40.2% risk reduction of disease progression or death in favour of IsaPd vs Pd. Although OS was considered immature at this stage, a trend towards longer OS in IsaPd (vs Pd) was observed (HR of 0.494; [95% CI; 0.240, 1.015]), with a median OS of 14.36 months in the Pd arm while in the IsaPd it had not been reached

The economic analysis evaluating the IsaPd as a 4L treatment is expected to yield 1.65 incremental discounted LYs and 0.96 incremental discounted QALYs compared with Pd. The projected gain in OS (1.940 years) was approximately 3 times the projected gain in PFS (0.643), reflecting a relatively large projected gain in PPS of 1.297 years. The incremental total costs of IsaPd are estimated to be XXXXXX. The ICER for IsaPd vs Pd is therefore estimated to be £125,948 per QALY gained.

In deterministic sensitivity analyses, in which input parameters were varied by ±25% of base case values, the ICER for IsaPd versus Pd was most sensitive to varying factors associated with medication costs. Scenario analyses indicated that using a set of favourable inputs for IsaPd yield ICERs of £60,090 vs Pd, while use of unfavourable inputs yield ICERs up to a maximum of £247,283. The mean ICERs from probabilistic sensitivity analyses were somewhat higher than the deterministic ICERs (£136,645 per QALY gained).

Considered as a whole, the results of these analyses suggest that even though IsaPd is projected to yield substantial improvements in LYs and QALYs gained vs. Pd, IsaPd is not likely to fall under the threshold value commonly accepted to represent cost-effectiveness by NICE (i.e. £50,000 per QALY gained). A key factor in the relatively high ICERs is the high cost of the companion product, pomalidomide. Because the use of IsaPd vs. Pd increases the duration of treatment in combination with pomalidomide relative to the duration of treatment of pomalidomide when used in monotherapy, the ICER for IsaPd vs. Pd is, by definition, likely to exceed the ICER threshold.

The main weakness in this evaluation is the immaturity of the key clinical outcomes data. At the time of the cut-off date (median follow-up time was 11.56 months in the IsaPd arm and 11.73 months in the Pd arm of the ICARIA-MM trial), 57% of PFS data on Pd and 44% of PFS data on IsaPd has progressed and form the evidence on which parametric extrapolations are based. The limited evidence available for OS is even more distinct since extrapolation long term to 15 years is based on 40% of deaths in Pd arm and 21%

of deaths on IsaPd. This is an unprecedented level of censoring and unlike any reported in other treatments appraised by NICE in the 4L setting. As OS drives the model results, these projections are associated with substantial uncertainty that are highly likely to have a material impact on estimates of cost-effectiveness.

This analysis is also subject to several other limitations, including those summarised below:

- PAS discounts for treatments other than isatuximab are not known and have been based on assumption in the analyses presented here. As the scenario analyses indicate that the ICER per QALY gained is sensitive to reduction in the pomalidomide discount and this uncertainty impacts significantly on the results.
- A number of the cost estimates for AEs were based on assumptions and introduce additional uncertainty into the model results.
- The proportion of IsaPd patients receiving G-CSF and RBC and platelet transfusions were assumed to be the same as that for Pd.
- The estimates of duration of treatment for subsequent therapies were estimated using a number of different sources that may have used different methods which might bias the calculations.
- Finally, there are inherent limitation with the PSM approach. Because the survival distributions for PFS, PFS on treatment, and OS are estimated independently the fitted distributions for one outcome may be inherently inconsistent with those for other outcomes (e.g., projected PFS may exceed projected OS, projected TTD may exceed projected PFS On Treatment). To account for this possibility, the distribution of PFS was constrained not to exceed that for OS and the distribution for TTD was constrained to not exceed PFS On treatment.

While the key OS data are immature for the purposes of HTA, the evidence from ICARIA-MM is a key strength of this economic appraisal. The endpoints of OS, PFS and TTD are directly relevant to NICE appraisal of health benefits, and the necessary assessment of incremental benefit required to justify incremental cost. That the comparator, pomalidomide, represents routine care for NHS patients in 4L setting is another notable strength for decision-making. The collection of patient-reported EQ-5D-5L within ICARIA-MM is a third. In many HTA decisions, when the clinical evidence necessarily falls short of these standards, understanding the incremental health benefit of innovative treatment is a far greater challenge. Here, the quality and relevance of clinical evidence to support economic appraisal is highly credible.

An alternative approach using average cost per progression-free month with IsaPd compared with DARA in the 4L setting was considered. Both these CD38 drugs have a similar list price but offer very different outcomes. Below a simplistic approach is presented in Table 64 which compares the cost per progression-free month using the median PFS to calculate average drug cost of treatment in a 73 kg adult patient and assuming 100% RDI for each drug. No administration costs are included.

The total cost of treating a 73 kg patient with daratumumab at its list price until progression (median PFS = 4 months) is £51,840. The average cost/progression-free month is £12,960. Table 64 shows the impact on the cost/progression-free month when the PAS discount is varied with daratumumab monotherapy (0%, 10%, 30%).

IsaPd, at the XXX PAS discount, and with the assumed XXX discount on pomalidomide, and median PFS of 13.3 months has a total cost of XXX XXX. If the discount on pomalidomide is assumed to be XXX, the total cost decreases to XXX XXX. The average cost/progression-free month ranges from XXX XXX (XXX PAS on Pd) to XXX XXX (XXX PAS on Pd) due to the longer time a patient is progression-free with IsaPd. Unlike the economic analysis which uses TTD to estimate drug cost, this simplistic analysis calculates drug cost based on PFS. The results highlight that, despite comparable costs of keeping a patient progression-free, IsaPd is unlikely to considered cost-effective within the current NICE framework because it is used in combination with another branded and high cost treatment.

Table 64: Cost of treatment based on PFS for DARA vs IsaPd combination

	DARA			IsaPd (XXX)	IsaPd (XXX)
ICER	**£53,804**			**>£100k**	**>£100k**
LYG	**2.54**			XXX	
QALY gained	**1.36**			XXX	
Incremental LYG vs Pd	**1.07**			XXX	
Incremental QALY vs Pd	**0.54**			XXX	
Median PFS (months)	**4**	**4**	**4**	**13.3**	**13.3**
Pomalidomide discount	**n/a**	**n/a**	**n/a**	XXX	XXX
CD-38 discount	**0%**	**10%**	**30%**	XXX	XXX
Drug cost per cycle					
Cycle 1	**£17,280**	**£15,552**	**£12,096**	XXX XX	XXX XX
Cycle 2	**£17,280**	**£15,552**	**£12,096**	XXX XX	XXX XX
Cycle 3-6	**£8,640**	**£7,776**	**£6,048**	XXX XX	XXX XX
Cycle 7+	**£4,320**	**£3,888**	**£3,024**	XXX XX	XXX XX
Total cost for PFS	**£51,840**	**£46,656**	**£36,288**	XXX XX	XXX XX
Average cost/progression-free month per patient	**£12,960**	**£11,664**	**£9,072**	XXX XX	XXX XX

Based on a 73 kg adult and 100% RDI. Daratumumab source TA510 (3). IsaPd (XXX) indicates XXX PAS on pomalidomide. IsaPd (XXX) indicates XXX PAS on pomalidomide.
Abbreviations: DARA, daratumumab monotherapy; ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab+ pomalidomide+ dexamethasone; LYG, life-year gained; Pd, pomalidomide+ dexamethasone; PFS, progression-free survival; QALY, quality-adjusted life-years.

Keeping in mind the limitations and considerations highlighted above, results of this analysis suggest that, for patients with RRMM, IsaPd treatment in 4L is likely to result in clinically meaningful gains in life expectancy and QALYs compared with Pd. However, largely due to the relatively high cost of Pom, IsaPd is not likely to be considered a cost-effective use of healthcare resources in the UK, based on thresholds for cost-effectiveness used by NICE to evaluate health technologies

The economic analysis should be viewed considering the improvements in clinical outcomes, challenge of meeting the cost-effectiveness threshold when pomalidomide has been accepted for use at the margin under the same threshold, the high level of censored data, and the resulting level of uncertainty.

Considering these factors, we strongly urge the committee to consider the CDF as an option for isatuximab to enable access for patients with high unmet need at 4L and to facilitate further data collection in order to reduce the uncertainty in outcomes for these UK-treated patients.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [ID1477]

Clarification questions

13 December 2019

File name	Version	Contains confidential information	Date
ID1477_Isatuximab_Response to Clarification questions_13122019_ FINAL_REDACTED	FINAL	Yes	13th December 2019

Section A: Clarification on effectiveness data and statistical analyses performed

A1. Priority. Please clarify the source of the additional single arm study for the relevant comparator for MAIC (Matching Adjusted Indirect Comparisons, Figure 11, page 29). Was this one of the 136 full text documents excluded for having an ineligible study design?

The single-arm study in Figure 11 refers to PANORAMA-2 (1). Unlike PANORAMA-1, this study was not identified via the first round of the systematic literature review search (because it was not a randomised controlled trial [RCT]), and, therefore, is not one of the 136 studies excluded due to ineligible study design.

During the network development phase, it emerged that there was a paucity of data on panobinostat, bortezomib, and dexamethasone (PanVd), particularly for lenalidomide refractory patients. So, in order to facilitate comparisons with this intervention, a single arm PANORAMA-2 trial was identified by Sanofi and included for the focused network. Overall 38% of patients in PANORAMA-1 compared to 98.2% of patients in PANORAMA-2 were Len refractory, suggesting the population in PANORAMA-2 is more similar to the ICARIA population (93.5% of the IsaPd arm and 91.5% for Pd arms respectively was Len refractory. Therefore, while PANORAMA-2 was not included in our first-round search (because it was not an RCT), PANORAMA-2 was later identified as a relevant study for this evaluation and included as a single-arm study.

A2. Priority. Please clarify which are the three studies considered of relevance to the submission (Figure 11, page 29), and in how many papers they were reported.

Three studies were reported in four sources:

PanVd

- San-Miguel JF, Hungria VTM, Yoon SS, Beksac M, Dimopoulos MA, Elghandour A, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: A multicentre, randomised, double-blind phase 3 trial. THE LANCET ONCOLOGY. 2014;15(11):1195-206 (2).

- Richardson PG, Hungria VTM, Yoon S-S, Beksac M, Dimopoulos MA, Elghandour A, et al. Panobinostat plus bortezomib and dexamethasone in previously treated multiple myeloma: outcomes by prior treatment. BLOOD. 2016;127(6):713-21 (3).

- Richardson PG, Schlossman RL, Alsina M, DM W, Coutre SE, Gasparetto C, et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. BLOOD. 2013;122(14):2331-7 (1).

IsaPd

- A single phase III RCT including isatuximab (isatuximab in combination with pomalidomide plus a low dose of dexamethasone: study EFC14335 (ICARIA-MM)). This study is now published and has been enclosed as a reference (Attal et al., 2013 (4))

A3. Priority. Please clarify the procedure used for data extraction for the systematic literature review of clinical effectiveness evidence. Further information required includes how many reviewers completed the extraction. If one, were extractions checked by another reviewer? If two, were they completed independently? How were differences resolved? Which data were extracted?

A data extraction sheet was developed as an Excel spreadsheet and reviewers piloted the form on a number of studies before progressing to full data extraction. Two reviewers independently extracted data from eligible publications. A third reviewer adjudicated any disagreements.

We extracted the following elements from the eligible trials:

- Trial details (bibliographic details)
- Trial characteristics
    - Study design
    - Study objective
    - Study phase
    - Number of participating centres and countries
    - Eligibility criteria (inclusion and exclusion criteria)
    - Primary and secondary outcomes
    - Number of patients randomised/analysed
    - Treatment & follow up duration
    - Data collection time points

- Patient baseline characteristics
    - Age
    - Gender
    - Disease stage (International Staging System [ISS]) or measures of severity
    - Time since diagnosis
    - Weight,
    - Body mass index,
    - Eastern Cooperative Oncology Group performance status
    - Cytogenetic features
    - Number of and details of prior treatments
    - Concomitant therapies
    - Lab tests, including lactate dehydrogenase (LDH), albumin and creatinine levels
    - Co-morbidities
- Details of intervention (details were captured separately for induction, maintenance, and combined therapy as far as possible)
    - Treatment
    - Dose
    - Regimen
    - Mode and frequency of administration
    - Details of permitted dose changes and permitted concomitant therapies
    - Duration of treatment
- Details of statistical analyses
- For each of the outcomes specified in Section 2.3 the following was extracted:
    - Outcome definition and how it was assessed
    - The unit of measurement
    - The number of patients included in the analysis
    - The size of the effect:
        - For dichotomous outcomes; absolute and relative risks (or odds ratios) and risk (or rate) differences
        - For continuous outcomes; the mean change and measure of variance from baseline (or at both baseline and final visit), or mean difference between treatments and a p value
        - For time-to-event analysis; the number of events in each arm, median time to event and a hazard ratio and p-value. Survival probabilities at 1 and 2 years were also extracted where reported

- Where data are reported graphically, every effort was made to digitise the relevant data, where possible.
- Where possible, absolute and relative data were extracted

- A measure of precision for each estimate of effect (95% confidence intervals, standard error or standard deviation)

For each outcome, data was collected at all time points reported.

A4. Table 5 (page 31) and Table 6 (page 33) of the company submission (CS) both specify that dexamethasone could be taken orally or IV in both the isatuximab, pomalidomide, low-dose dexamethasone (IsaPd) and pomalidomide, low-dose dexamethasone (Pd) arms of ICARIA-MM. Please clarify the number and proportion of patients in each arm (of the overall population and of the 4th line post hoc analysis subgroup) who received dexamethasone IV and whether this was considered within the model.

Table 1 provides the number and proportion of patients in each arm (of the overall population) who received dexamethasone intravenous (IV) and oral.

Table 1: ITT population – dexamethasone distribution

Route of Administration	IsaPd, n (%) n=152	Pd, n (%) n=149
Injection	2 (1.32)	0 (0.00)
Oral	93 (61.18)	145 (97.32)
Injection & oral	57(37.50)	4 (2.68)

Abbreviations: IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ITT, intention-to-treat; Pd, pomalidomide, low-dose dexamethasone.

Table 2 provides the number and proportion of patients in each arm (of the 4th line [4L] population) who received dexamethasone IV and oral.

Table 2: 4L population - dexamethasone distribution

Route of Administration	IsaPd, n (%) n=51	Pd, n (%) n=58
Injection	1 (1.96)	0 (0.00)
Oral	26 (50.98)	58 (100.00)
Injection & oral	24 (47.06)	0 (0.00)

Abbreviations: 4L, fourth line; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; Pd, pomalidomide, low-dose dexamethasone.

The prior version of the model assumed that patients receiving IsaPd or Pd exclusively received oral dexamethasone. The assumption was made that oral route was the preferred route and dexamethasone would only be administered IV if oral administration was infeasible. Furthermore, because IV administration costs would not be counted separately from that for isatuximab, it was reasoned that costs for IV administration would actually be lower than those for oral, and therefore, more conservative. However, to increase the accuracy of our estimation, we have updated the model to reflect the distribution of oral/IV administration in the 4L patient population, as highlighted in Table 2 above.

For the purposes of determining the percentage of dexamethasone administrations that were oral/IV, a 50/50 split was assumed for the "Injection and oral" category (i.e., of the 24 patients who received both IV and oral dexamethasone, each was assumed to receive an IV administration 50% of the time). The resultant percentages of administration methods are shown in the Table 3.

Table 3: Percentages of administration routes used in the model

Route of administration used in the model	IsaPd (%)	Pd (%)
Injection	25.5%	0%
Oral	74.5%	100%

Abbreviations: IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; Pd, pomalidomide, low-dose dexamethasone.

In addition to the breakout of dexamethasone into oral/IV administrations, a new addition to the model was made to account for the reduction in recommended dexamethasone dose for those 75 years or older (from 40 mg to 20 mg). The percentage of individuals ≥75 years of age in each arm of the ICARIA-MM trial was calculated and shown below (Table 4). Note: this dose reduction was applied only to the IsaPd and Pd strategies and not to PanVd, as the dexamethasone dose in this strategy is already 20 mg, and it was assumed no dose reduction would occur.

Table 4: Patient distribution in the ICARIA-MM age strata <75 years and ≥75 years

ICARIA-MM patient population (4L)	IsaPd (%)	Pd (%)
<75 years (receiving 40 mg dex)	86.5%	84.5%
≥75 years (receiving 20 mg dex)	13.5%	15.5%

Abbreviations: dex, dexamethasone; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; Pd, pomalidomide, low-dose dexamethasone.

A5. Please clarify whether the 4th line *post hoc* analysis subgroup used intention-to-treat (ITT) data or '*safety population*' data?

The 4L post-hoc analysis used the intention-to-treat (ITT) data.

A6. In Table 8 (page 44), please clarify why the proportion of patients in both the IsaPD and the PD arms that was refractory to lenalidomide was not 100%, given that the inclusion criteria of the ICARIA-MM trial specify that patients must have had prior lenalidomide and subsequent progression.

The inclusion criteria state that patients had to have received at least two prior lines of anti-myeloma therapy, which included at least two consecutives cycles of lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) given alone or in combination. In ICARIA-MM, all patients had prior exposure to lenalidomide.

This is further expanded on by inclusion criterion 4 from the ICARIA-MM trial which also states:

Patients who have failed treatment with lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) alone or in combination, defined by any of the following:

- Progression had occurred while on or within 60 days from end of the treatment with lenalidomide and/or a proteasome inhibitor
- In case of previous response to lenalidomide and/or a proteasome inhibitor, patient had progressed within 6 months after discontinuation of the treatment
- Patients who had developed intolerable toxicity after a minimum of two consecutive cycles of a regimen containing lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) alone or in combination

Inclusion criteria 5 states that patients had to have progressed on or within 60 days after end of the previous therapy before study entry, i.e., refractory to the last line of treatment. This patient population included the following two categories:

- Refractory disease: patients who were refractory to all previous lines of treatment but had achieved at least a minimal response (MR) in one previous line.

- Relapsed and refractory disease: patients who were relapsed from at least one previous line of treatment and refractory to the last line of treatment. Patients could have been refractory to other previous line/lines of treatment.

Therefore, based on the inclusion criteria highlighted above, all patients had to have received lenalidomide (defined by inclusion criterion 4) however not all patients had to be *refractory* to lenalidomide at baseline. As such, Table 9 (page 44) reports 100% relapsed and refractory, and lower percentage who were refractory to lenalidomide.

A7. In Table 13 (page 54), please clarify why there is a difference between the IsaPd and Pd arms of ICARIA-MM in the number and proportion of patients not evaluable/not assessed for BOR (with over twice the number/proportion not evaluable/assessed in the Pd arm). Please clarify whether there was a biological reason for this difference.

On the IsaPd arm there were 7 patients who were recorded as not evaluable/not assessed for BOR. Four of these patients were recorded as 'non evaluable' because of missing M-protein data required for the independent review committee (IRC) to assess response. In all these cases patients were on treatment for less than one month (in some cases less than one week). Therefore, these cases were classified as non-evaluable. The remaining cases were not assessed by the IRC due to withdrawal of consent or death.

In the case of Pd, there were 16 cases in total that were not evaluable/not assessed for BOR. Four of these were non-evaluable because of missing M-protein data required by the independent review committee (IRC) or because patients were on treatment for less than one month (in some cases less than one week). The remaining cases were not assessed due to the short length of time patients were on treatment.

Therefore, to the best of our knowledge there is no biological reason for this difference. Instead this was the nature of the trial conduct and reporting of outcomes.

A8. Please clarify the method/s used for assessing adverse events.

Treatment-emergent (TE) adverse events (AE) data were collected from the time of signed informed consent to 30 days following the last administration of study treatment. After the 30-day end of treatment visit, all ongoing related AEs, all ongoing SAEs whatever the relationship with study treatment, and all new related AEs regardless of seriousness, were reported and followed until resolution or stabilisation. All AEs were graded according to National Cancer Institute Common Terminology for Adverse Events (NCI-CTCAE) v4.03.

Treatment-emergent AEs were defined as AEs that developed, worsened (according to the Investigator opinion), or became serious during the TEAE period.

- Infusion reactions (IR)

Whenever possible, a clinical diagnosis of the IR (e.g., cytokine release syndrome, infusion related reaction, anaphylactic reaction, hypersensitivity) was reported by the Investigator in a specific AE page instead of its individual symptoms. In addition, symptoms of IR were reported on a separate electronic case report form (eCRF) form.

Infusion reactions were analysed using the Investigator reported term collected in the specific AE forms. Additional analyses were performed based on any TEAEs occurring within 24 hours of an infusion (16 1 9 sap [2.1.4.1]).

- Adverse events of special interest (AESI)

The AESIs in the study included Grade ≥3 IRs, and reports of pregnancy, symptomatic overdose with study treatment (isatuximab, pomalidomide or dexamethasone), and second primary malignancy.

Statistical considerations

The primary focus of AE analyses was on TEAEs. Pre-treatment and post-treatment adverse events were described separately. Unless otherwise specified, TEAEs analysed by system organ class (SOC) and preferred term (PT) were sorted by the internationally agreed SOC order and in decreasing frequency of PTs in the IsaPd arm within SOCs. The AE incidence tables were presented by primary SOC, high-level group term (HLGT), high-level term (HLT), and PT and sorted by SOC internationally agreed order and by alphabetic order of HLGT, HLT, and PT, using the version 21.0 of Medical Dictionary for Regulatory Activities (MedDRA).

Summaries were provided for all TEAEs (all grade and Grade ≥3), drug-related TEAEs, fatal AEs, serious TEAEs, drug-related serious TEAEs, TEAEs leading to definitive treatment discontinuation, TEAEs leading to premature treatment discontinuation (isatuximab, pomalidomide, or dexamethasone), TEAEs leading to dose modifications (reductions, delays, treatment interruptions), and pre and post-treatment AEs. For patients with multiple occurrences of the same AE within the observation period, the maximum severity grade was used.

Premature treatment discontinuation was defined as the discontinuation of at least one of the study treatments and continuation of at least one study treatment. Definitive treatment discontinuation was defined as the discontinuation of all the study treatments or of the last ongoing study treatment.

Cause of death was analysed by study period (on-treatment, post-treatment). Summary was provided for AEs leading to death in context of disease progression and in the context other than disease progression (death within 30 days from last study treatment administration and for whom cause of death was not disease progression or death occurred more than 30 days from last study treatment administration and the cause of death was AE).

Additional analyses were provided for the following other significant events.

Infusion Reactions

The following analyses were performed:

- Number (%) of patients experiencing IRs according to Investigator reported AEs presented by primary SOC and PT (both sorted by decreasing order of frequency) summarised by grades (all grades and by grade).

- Description of the IRs (according to Investigator reporting): incidence, action taken, timing (number of infusions at first occurrence of IR), duration, description of symptoms of IRs

- Additional summary tables were provided by SOC and PT: any TEAEs occurring within 24 hours from the start of any isatuximab infusion, any TEAEs occurring within the 24 hours and from the "Hypersensitivity and CRS" CMQ, any TEAEs (not only limited to those occurring within 24 hours of any isatuximab infusion) and from the "Hypersensitivity and CRS" CMQ

Other significant AEs

To further assess potential risks, the following other significant AE were assessed:

- IRs (including cytokine release syndrome; see above)
- Second primary malignancies
- Respiratory AEs (Lower respiratory AEs and respiratory infections)
- Neutropenia and neutropenic complications

- Infections
- Thrombocytopenia and haemorrhages
- Tumour lysis syndrome (TLS)
- Haemolytic disorders and blood cell (red blood cells and platelet) transfusions
- Autoimmune disorders
- Pregnancy
- Symptomatic overdose with study treatment

Analysis of pregnancy and symptomatic overdose was based on AESI reporting only. For the analysis of the remaining other significant AEs, groupings were defined using Customized MedDRA Queries (CMQs) or were derived from the laboratory data

A9. Please provide PDFs of the excluded publications from Table 3 of Appendix D that are listed at the end of this clarification question document.

These are provided separately.

A10. Please clarify whether there was a biological reason for the greater proportion of patients in the IsaPd arm than the Pd arm experiencing injury, poisoning and/or procedural complications (Appendix G, Table 6, page 110).

There was a formatting error in the section of the table reporting the injury, poisoning and/or procedural complications in Appendix G, Table 6 of the CS. 'Infusion related reaction' and 'fall' are sub-categories of 'injury, poisoning and/or procedural complications' and with an incidence ≥5% in any treatment group by Primary system organ class (SOC) and preferred term (PT).

Table 5 below shows greater proportion of patients experiencing injury, poisoning and/or procedural complications in the IsaPd arm (47.4%) compared to the Pd arm (11.4%). This is due to the difference in administration of the two drugs and the level of infusion related reactions in the IsaPd arm. If the Infusion related reactions were excluded, the level of patients experiencing injury, poisoning and/or procedural complications would be similar.

Table 5: ICARIA-MM safety outcomes – Proportion of patients experiencing injury, poisoning and/or procedural complications

	Pd (N=149)		IsaPd (N=152)	
Primary System Organ Class Preferred Term, n (%)	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
Injury, poisoning and procedural complications	17 (11.4)	1 (0.7)	72 (47.4)	8 (5.3)
Infusion related reaction	2 (1.3)	0	56 (36.8)	4 (2.6)
Fall	8 (5.4)	1 (0.7)	8 (5.3)	0

Abbreviations: IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; MM, multiple myeloma; Pd, pomalidomide, low-dose dexamethasone; PT, Preferred term; TEAE, Treatment emergent adverse event; SOC, System organ class; MedDRA 21.0.
n (%) = number and percentage of patients with at least one TEAE.
Note: Table sorted by SOC internationally agreed order and by decreasing frequency of PT for all grades in IsaPd group. Only SOC with at least one PT >= 5% in at least one treatment group are presented.

A11. Please clarify whether the entire EORTC-QLQ-C30 questionnaire was administered to patients in the ICARIA-MM trial, and what the effects of IsaPd (vs. Pd) were on the social, emotional and cognitive subscales.

Yes, the entire European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) was administered to the patients who completed it at the study centre prior to discussing their health/disease status, and prior to study treatment administration, or other study-related procedures on Day 1 of every cycle, at the EOT visit, and 60 days (±5 days) after last study treatment administration. The time estimated to complete the EORTC QLQ-C30 was approximately 10-15 minutes.

The effect of IsaPd vs Pd in 4L patients and in the three subscales requested are shown below (Figure 1, Figure 2 and Figure 3).

Figure 1: Cognitive functioning – QLQ-30 – Mean change from baseline and 95% CI for cognitive functioning over time – safety population evaluable for cognitive functioning

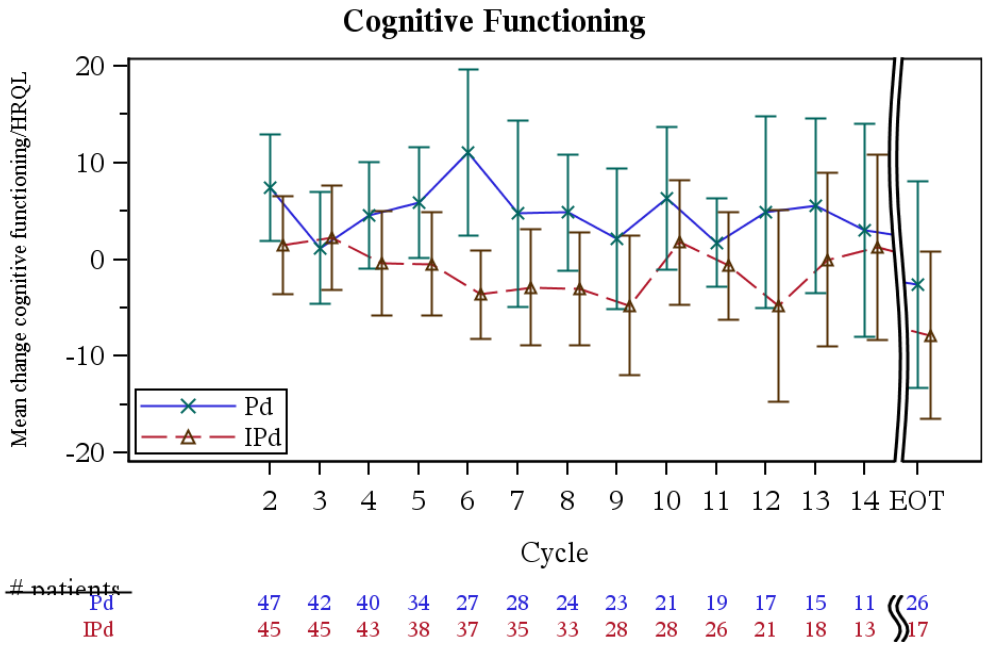


Figure 2: Social functioning – QLQ-30 – Mean change from baseline and 95% CI for social functioning over time – safety population evaluable for social functioning

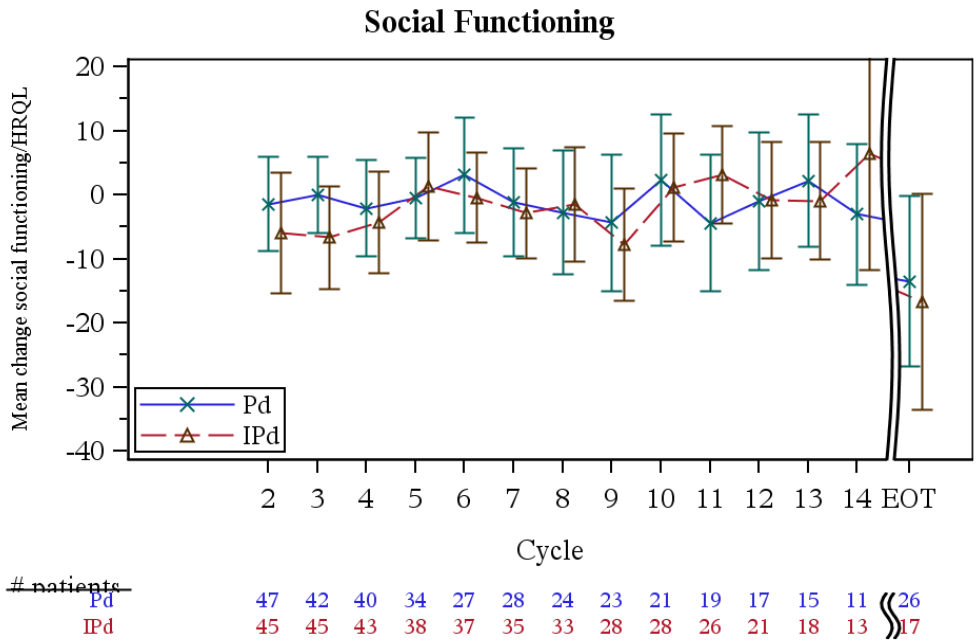
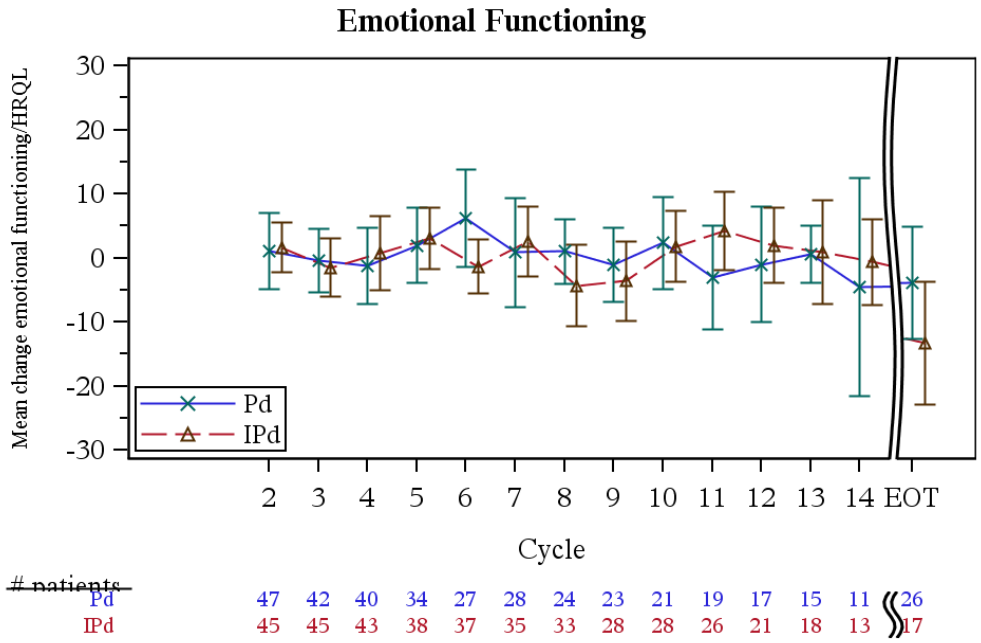


Figure 3: Emotional functioning – QLQ-30 – Mean change from baseline and 95% CI for emotional functioning over time – safety population evaluable for emotional functioning



A12 CS, Table 10. Please clarify why stratification for age was by age <75 years vs ≥75 years but the pre-specified subgroups for age were <65, 65-74 and ≥75years.

Age over 75 years is a prognostic factor and the dose of dexamethasone is different in such patients thus randomisation was stratified on age using 2 categories, < 75 years and >= 75 years, in order to balance treatment arms in these age categories. Moreover, we used 2 categories and not 3 for stratification in order to limit the number of strata and avoid incomplete blocks in randomisation scheme that could result in an imbalance between arms. For subgroup analyses, it seemed more relevant to us to evaluate the consistency of results across age using 3 categories and it is the usual way to report results in multiple myeloma (MM).

A13 CS, Table 10. Subgroup and multivariable analyses.

(i) Please rerun the multivariable analysis

- **leaving in the model the stratification factors and any known prognostic factors irrespective of their statistical significance and baseline balance.**
- **Include other potential prognostic factors using criteria other than simply statistical significance, including the magnitude of effect and expert opinion.**
- **Include covariates that are continuous variables (such as age) as continuous variables and assess their relevance using appropriate non-linear relationships.**

Please refer to Frank Harrell Regression Modelling strategies (2001)

Please see below (Table 6) the multivariate analyses with all variables as well as the age, creatinine clearance (CrCl) and number of previous lines of therapy as continuous variables. Please note we have no hazard ratio (HR) for “Region (geographical): Asia vs Western Europe” because this is redundant with “Race: Asian vs White” information.

Table 6. PFS – primary analysis based on disease assessment by the IRC by treatment population – ITT population - Multivariate analyses with all variables as well as the age and CrCl as continuous variables

Prognostic factors	Hazard ratio (95% CI)	P-value
Treatment: IsaPd vs Pd	0.443 (0.298 to 0.659)	<0.0001
Age (as per CRF)	1.195 (0.942 to 1.516)	0.1412
Age^2	0.999 (0.997 to 1.000)	0.1176
Baseline creatinine clearance (MDRD formula) in mL/min/1.73m2	0.956 (0.921 to 0.992)	0.0165
Baseline creatinine $clearance^2$	1.000 (1.000 to 1.000)	0.0157
Number of previous lines of therapy	1.093 (0.683 to 1.748)	0.7113
Number of previous lines of $therapy^2$	0.999 (0.958 to 1.043)	0.9774
Gender: Female vs Male	0.789 (0.526 to 1.184)	0.2527
Race: Asian vs White	0.691 (0.250 to 1.910)	0.4766
Race: Other vs White	28.455 (4.298 to 188.403)	0.0005
Region (geographical): Eastern Europe vs Western Europe	1.361 (0.520 to 3.565)	0.5305
Region (geographical): North America vs Western Europe	0.573 (0.141 to 2.327)	0.4357
Region (geographical): Asia vs Western Europe	-	.
Region (geographical): Other countries vs Western Europe	1.064 (0.517 to 2.187)	0.8670
Region (regulatory): Other countries vs Western countries	1.591 (0.745 to 3.399)	0.2305
Baseline ECOG PS: 2 vs (0 or 1)	1.768 (0.993 to 3.147)	0.0527
ISS staging at study entry: II vs I	1.631 (0.854 to 3.114)	0.1382
ISS staging at study entry: III vs I	1.439 (0.656 to 3.157)	0.3643
R-ISS staging at study entry: II vs I	1.103 (0.540 to 2.256)	0.7877
R-ISS staging at study entry: III vs I	2.576 (0.855 to 7.757)	0.0926
Cytogenetic abnormality (del(17p), t(4;14), t(14;16)): At least one vs None	2.326 (1.147 to 4.717)	0.0192
Cytogenetic abnormality (del(17p), t(4;14), t(14;16)): Unknown vs None	0.866 (0.205 to 3.649)	0.8443
Cytogenetic abnormality del(17p): Yes vs No	0.638 (0.284 to 1.433)	0.2762
MM type at diagnosis: IgG vs Non-IgG	0.856 (0.572 to 1.282)	0.4511
Refractory to lenalidomide: Yes vs No	3.961 (1.219 to 12.867)	0.0221
Refractory to PI: Yes vs No	1.274 (0.797 to 2.036)	0.3111

ii) Please clarify whether the company's subgroup analysis was conducted using a model that included the stratification factors (irrespective of whether they were statistically significant) and all known prognostic and predictive variables. For other pre specified factors that are not known to be prognostic or predictive, please assess their relevance using full and reduced models together with their interactions with treatment.

The sub-group analyses were not stratified nor adjusted. The rationale behind this strategy was to be simple and robust. Stratification on some factors would result in very small sample size for some of the subgroups. For example, there would be a very small sample size in the stratum "Age >= 75 years" and stratum "> 3 prior lines" and also in some categories of prognostic factors.

A14. CS, Table 10. Please clarify why it was necessary to adjust the secondary endpoint OS for an interim analysis, Please provide a justification for using Inverse Probability of Censoring Weighting (IPCW) to adjust for treatment switching.

It was necessary to adjust the OS for the interim analysis in order to take into account subsequent therapy with daratumumab. A sensitivity analysis was performed where OS was adjusted for switching to daratumumab as a subsequent treatment using the inverse probability of censoring weighting (IPCW) method. To estimate the treatment effect in the absence of a switch to subsequent anti-cancer therapy with daratumumab, a sensitivity analysis using the IPCW method was performed. Overall, in the IPCW analysis, patients were weighted according to the probability of switching to daratumumab based on the values of prognostic covariates at baseline and over time and patients switching to daratumumab were censored at the time of the switch. Patients who did not receive daratumumab and had characteristics similar to patients who received daratumumab were weighted more highly. Region of the world and disease response over time were identified as the main factors contributing to shift to daratumumab.

The trend towards longer OS on each study arm, particularly pomalidomide, should be interpreted in the context of the subsequent therapy, in particular with daratumumab, given after definitive treatment discontinuation. At the analysis cut-off date, 45 (54.2%) of the 83 patients in the Pd arm receiving subsequent treatment had received daratumumab (other anti-CD38) therapy. In addition, 6 patients in the IsaPd arm received daratumumab after definitive treatment discontinuation.

A15. CS, Page 52. Please confirm that the stratified hazard ratio is stratified only by age.

No. All efficacy analyses were performed on the ITT population. All analyses using the stratification factors were performed using the stratification factors as per IRT. The stratification factors are: age and number of previous lines of therapy.

A16. CS, page 52. Please provide results of an analysis of PFS including stratification factors, all known prognostic factors, and a model that allows for an assessment of the differential effect by line of treatment (i.e. with an interaction term).

Please see below the analysis of PFS requested (Table 7).

Table 7: PFS – primary analysis based on disease assessment by the IRC by treatment population – ITT population

Progression Free Survival based on IRC	Pd (N=153)	IsaPd (N=154)
Number (%) of events	89 (58.2)	73 (47.4)
Number (%) of patients censored	64 (41.8)	81 (52.6)
Kaplan-Meier estimates of PFS in months		
25% quantile (95% CI)	2.76 (1.971 to 3.055)	4.27 (3.088 to 5.848)
Median (95% CI)	6.47 (4.468 to 8.279)	11.53 (8.936 to 13.897)
75% quantile (95% CI)	NC (10.382 to NC)	NC (14.784 to NC)
Comparison vs. Pd		
Stratified[a] Log-Rank test p-value[b] vs Pd	-	0.0011
Stratified[a] Hazard ratio (95% CI) vs Pd	-	0.489 (0.348 to 0.687)
Interaction P-value	-	0.6787
PFS probability (95% CI)[c]		
2 Months	0.801 (0.723 to 0.859)	0.910 (0.850 to 0.947)
4 Months	0.617 (0.529 to 0.694)	0.760 (0.681 to 0.822)
6 Months	0.506 (0.417 to 0.588)	0.665 (0.580 to 0.737)

Progression Free Survival based on IRC	**Pd (N=153)**	**IsaPd (N=154)**
8 Months	0.432 (0.345 to 0.516)	0.620 (0.534 to 0.695)
10 Months	0.369 (0.284 to 0.453)	0.547 (0.459 to 0.627)
12 Months	0.296 (0.213 to 0.384)	0.476 (0.380 to 0.566)
14 Months	0.259 (0.174 to 0.351)	0.387 (0.277 to 0.495)
Number of patients at risk[c]		
2 Months	105	129
4 Months	80	106
6 Months	63	89
8 Months	51	81
10 Months	33	52
12 Months	17	30
14 Months	5	14

A17. CS, Page 101 + 106. Please clarify what is meant by "*… an estimated treatment effect for each of four different treatment effect assumptions (i.e., constant shift in survival time, accelerated failure time, PH, and proportional odds) were applied to failure times in the control group to obtain a counterfactual KM survival distribution for the control group reflecting the expected outcome had those patients received study treatment with the specified treatment effect assumption*." Please provide a comparison of models that do not assume a constant treatment effect either 1) a single model fitted to the data with appropriate terms that allow for time-varying treatment effects, or 2) separate models fitted to each treatment arm.

The first point relates to the treatment effect diagnostic plots used to assess the parametric survival distributions. These plots were obtained by comparing the KM curve for the active arm with an "adjusted" curve for the control arm obtained by adjusting either the failure times (for shift or constant accelerated failure time models) or the hazard rates or odds of events over time (for proportional hazards and proportional odds) of the control arm by a constant factor to minimize the difference between the active and "adjusted" control arm Kaplan-Meier curves.

While we are uncertain what the ERG means by "provide a comparison", it should be noted that the "unrestricted" survival distributions, which allow for all the parameters of the survival distributions to vary for the 2 treatments, are effectively "separate models for each treatment arm" and therefore allow for the possibility of time-varying treatment effects when expressed as hazard ratios or acceleration factors. In comparison, for the "restricted" survival distributions, only one parameter of the distribution differs across the treatment groups (such as the scale parameter for a Weibull distribution) and hence employ constant treatment effects.

A18. CS, Page 102. Please provide evidence for the clinical plausibility that the hazards are constant and proportional over the 15-year time horizon of the model.

The clinical experts who were asked to comment on the plausibility of the extrapolations did not raise any concerns with the assumption of constant and proportional hazards over the time horizon.

A19. CS Figures 22 and 26. The ERG is unable to interpret the BIC values without clarification of how the models were fitted to the data in each treatment group and the assumptions that were made. Please provide more detail about model fit and assumptions.

As described in section B.3.3.1 of the submission, estimates of PFS, TTD, PFS on treatment, and OS for IsaPd and Pd were derived by fitting parametric survival distributions

based on maximum likelihood estimation using the flexsurv R package (Links: Source Code, Documentation, Journal of Statistical Software Publication).

Each model was fitted based on a dataset containing survival data for both arms. This dataset includes one row per observation and columns for time (event/censor time), flag (1=event, 0=censor), and treatment (the treatment arm represented by this observation). An example of this dataset structure is shown below (Table 8) with dummy data for illustrative purposes.

Table 8: Example TTE analysis dataset format

Time (months)	Flag	Treatment
13.2	1	"Treatment A"
15.6	0	"Treatment A"
23.4	0	"Treatment B"
7.5	1	"Treatment B"

Abbreviations: TTE, time to event.

For each parametric distribution considered (e.g. Weibull, Lognormal, etc.), two types of models were fitted:

- Restricted: the effect of treatment is assumed to impact only the designated "location" parameter of the distribution (e.g. the scale parameter of the Weibull distribution). The location parameter varies from distribution to distribution but is determined by the flexsurv package and is generally the one that corresponds to some kind of intuitive treatment effect model (e.g. proportional hazards, accelerated failure time, etc…).
- Unrestricted: the effect of treatment is assumed to impact all parameters of the distribution (e.g. the shape and scale parameters). This approach yields estimates that are equivalent to fitting the given parametric distribution separately to data from each arm, but ensures that it models the same exact observations as the equivalent restricted model and therefore may be compared head-to-head with the restricted model using fit statistics such as BIC.

For example, a restricted Weibull model would be fitted using the following syntax, where the yellow highlighted section denotes the covariate being applied to the location parameter of the Weibull model:

```
restricted_model <- flexsurvreg(
        Surv(time, flag)~treatment,
```

```
        data = analysis_dataset,
        dist = “weibull”
    )
```

An unrestricted Weibull model would be fitted using the syntax below, where the yellow highlighted section shows the same covariate additionally being applied to the shape parameter to ensure that it is also impacted by treatment.

```
    unrestricted_model <- flexsurvreg(
        Surv(time, flag)~treatment,
        data = analysis_dataset,
        dist = “weibull”,
        aux = list(shape = ~treatment)
    )
```

Since these models are fitted to the exact same analysis dataset and model likelihood for the exact same observations, they will yield estimates of BIC which are comparable and reflect the fit of the two models as well as their differing degrees of freedom.

Since this approach includes both arms in a single model, it requires that both arms have the same parametric form. This requires the assumption that, among the set of parametric forms considered, at least one will provide an acceptable fit. Given the number of distributions considered, including the highly flexible restricted cubic spline models, and that additional distributions can be added if no good fit is found, we believe this assumption to be reasonable.

Further, we believe that there are substantial problems associated with selecting different distributional forms for the two treatment arms. Different distributional forms allow for different possibilities in terms of the potential shape of survival distributions and associated hazard functions. For example, an exponential distribution will necessarily assume constant hazards and rule out any possibility of a long-term trend of decreasing hazards.

The approach the selecting different parametric forms for different arms puts this question to the researcher. The researcher must decide whether one arm has the possibility of a long-tail or not.

By contrast, the approach of requiring that the same distributional form be used across treatment arms requires that the data resolve this question. The researcher still plays a role

in selecting the distributional form that will define a universal of possible survival curves for both arms, but the data, not the researcher, determines which of those possibilities are realised for each arm. We believe this data-driven approach is preferable.

For more information on the flexsurv package, supported distributions, and parameterisations, we would refer you to the package source code, documentation, and publication.

A20. CS, Page 106. Please clarify the criteria by which the three clinical experts made their judgment on the most appropriate model.

The three clinical experts were shown selected OS and PFS (Figure 3) curves fitted to the 4th line patient-level data collected during the ICARIA-MM trial's follow-up period. They were also shown extrapolations of OS and PFS curves to 15 years (i.e. the maximum life expectancy of patients with RRMM who are on 4th line therapy). The OS and PFS extrapolation curves shown to the KOLs were

- Exponential
- log-normal R)
- Log-logistic (R)
- Weibull (R)
- Gompertz (Restricted)
- Gen-gamma (Restricted)
- Lognormal (Unrestricted)
- RSC Weibull (Restricted)
- Log-logistic (Restricted)
- RCS Lognormal (Restricted)
- Gen. F (Restricted).

For OS extrapolations, the KOLs were asked the following questions:

By looking at the extrapolation period (i.e. between 18 to 180 months) in the OS curves, do the survival projections after 18 months appear to be clinically plausible for RRMM patients on 4th line therapy? Do any of the OS curves seem to reflect clinical experience?

- *If not, what would a clinically plausible extrapolation look like?*
- *Which OS curve do you think is clinically most plausible?*

For the PFS extrapolations, the KOLs were asked the following questions:

By looking at the extrapolation period (i.e. between 18 to 180 months) in the PFS curves, do you think the PFS curves are clinically plausible (i.e. reflect clinical experience) for RRMM patients on 4th line therapy?

- *If not, what would a clinically plausible extrapolation look like?*

Below (Table 9 and Table 10) we provide the responses as recorded from the clinical experts regarding 4L extrapolations.

Table 9: Clinical expert opinion preference of extrapolations for overall survival

KOL 1	KOL 2	KOL 3
Weibull (R)	Weibull (R)	Exponential
Gompertz (R)	Gompertz (R) (but not great)	Weibull (R)
Lognormal (U)		

Table 10: Clinical expert opinion preference of extrapolations for progression-free survival

KOL 1	KOL 2	KOL 3
RCS Weibull (R)	Weibull (R)	Exponential
Exponential	Gompertz (R)	RSC Weibull (R)
Weibull (R)/Log-logistic (R)		

Full details on experts' comments on the shape and the tail of the fitted parametric curves, if required, are available on request.

A21. CS, Page 106. Please clarify whether the choice of model assume a constant treatment effect (i.e. constant acceleration factor) or allows for the possibility of a non-constant effect over time.

- Model assumes constant acceleration factor
- Exponential is constant acceleration and constant PH
- Model does allow for non-constant effects over time, can incorporate different families of different distributions or unrestricted models, and allow users to enter empirical distribution into the model.

A22. Appendix, Page 281. The CS states, "*The level of heterogeneity was assessed qualitatively by visually inspecting Kaplan-Meier curves for PFS, comparing KM% at 6 and 12 months (insufficient data for a comparison at 18 months), via Cox Proportional Hazards hazard ratio estimate, using the Mantel-Haenszel test to compare survival curves.*" Please clarify how heterogeneity was assessed using Kaplan-Meier survival functions. Please clarify how it was decided which variables to include in Cox models and whether interaction and higher order terms were included.

The visual inspection of Kaplan-Meier (KM) curves allowed us to compare arms from different studies containing the same treatment. If the KM curves for these arms were to differ substantially (as was the case for the PanVd arms in PANORAMA-1 and PANORAMA-2), that provides an initial indication that the studies may not be comparable.

Regarding the Cox proportional hazards analyses, we did not include any covariates in these. Apart from the Sanofi sponsored studies, we did not have access to individual patient data (IPD), but only overall KM data reported by arm. Therefore, the Cox regression could not include any covariates (and consequently no interaction terms). Instead, it was done on the KM data for all arms of the same treatment, using study as an explanatory variable.

Section B: Clarification on cost-effectiveness data

B1. Priority. Please provide a revised base case (deterministic and probabilistic) in the light of any changes made in response to the clarification questions (e.g. including but not limited to response to B3.

Summary of changes made to the revised base case, following review of the ERG clarification questions are shown in Table 11. For this section of the clarification question we present results for the ERG preferred case (with correction of Calculations for Application of Terminal Decrement and Requested Edits to Inputs Except Removal of PAS shown) and Sanofi revised based which is exactly the same as the ERG preferred case, except for inclusion of assumed PAS for the comparators.

Table 11: Summary table comparing original model to revised model

Updated made based on ERG requests		
Original Sanofi base case	**ERG preferred case**	**Sanofi revised base case**
Assumed PAS discounts on pomalidomide, daratumumab and panobinostat	No PAS discounts on pomalidomide, daratumumab and panobinostat	Assumed PAS discounts on pomalidomide, daratumumab and panobinostat
Oral dexamethasone use assumed for all patients as conservative assumption	Dexamethasone distribution from ICARIA has been applied to account for patients taking oral and/ IV dexamethasone	
Utility from ICARIA for PFS off treatment and PPS off treatment used	Utility for PFS and PD independent of whether on or off treatment [see B3]	
Application of time for PFS and PD on and off treatment based on ICARIA	Removed the estimated Mean Duration of Post-Progression Treatment (Months) (Cells D21:E23 in the 'Costs-Other' Worksheet). [see B3]	
Error regarding the calculation of death	Error corrected	
Age- and sex-matched general population mortality rates in the UK derived from Office for National Statistics. England, Interim Life Tables, 2015-2017	Age- and sex-matched general population mortality rates in the UK derived from Office for National Statistics. England, Interim Life Tables, 2016-2018	
Uses 365 days for annual year	Uses 365.25 for annual year [B29 and B30]	

Sanofi-identified errors (based on ERG clarification questions)		
Original base case	**Revised base case**	**Sanofi revised base case**
Granulocyte colony stimulating factor (GCSF), red blood cell (RBC) and platelets transfusions use in the model were based on published data for Pd.	Granulocyte colony stimulating factor (GCSF), red blood cell (RBC) and platelets transfusions are now based on 4L ICARIA patients	
Utility for PanVd were assumed to be the same as Pd, while subsequent treatments in PanVd were assumed to be the same as IsaPd	Utility for PanVd were assumed to be the same as IsaPd	
Dexamethasone counted as premedication and as part of IsaPd costs – error in terms of downloading	We have corrected this error and costed dexamethasone as part of IsaPd. Dexamethasone costs were removed from pre-medications to avoid double counting.	
An additional error was identified in the calculations of the one-off cost associated with progression. However, in the UK base case, no one-off costs have been applied for cost of progression.	This calculation has been corrected in the revised version of the model. Since these costs are zero in all analyses, this correction has no effect on the results.	

B2. Priority. In accordance with NICE process please provide analyses that do not assume a Patient Access scheme for comparator interventions for the company base case and sensitivity analyses both for the base case in the company submission and any updated analyses in response to the clarification questions.

Below (Table 12) are revised results shown all other changes to the model with the exception of the removal of the PAS for the comparators (Sanofi revised base case).

Table 12: Summary base-case results following correction of calculations for application of terminal decrement and requested edits to inputs except removal of PAS (i.e. Sanofi revised base case with all PAS included) *

Outcome	IsaPd	Pd	PanVd
Totals, discounted			
Costs (£)	[redacted]	[redacted]	[redacted]
LYs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Difference (IsaPd) vs. Comparator			
Costs (£)		111,228	136,126
LYs		1.649	1.144
QALYs		1.071	0.849
ICER (IsaPd) vs. Comparator			
Cost (£) per life-year saved		67,465	118,959
Cost (£) per QALY saved		103,842	160,387

* includes PAS for Isa ([redacted]), Pd ([redacted]), Panobinostat ([redacted]) and daratumumab ([redacted])

Below are revised results (base-case (Table 13) and sensitivity analyses (Table 14)) shown with all other changes to the model as well as the removal of the PAS for the comparators at the request of the ERG.

Table 13: Summary base case results following correction of calculations for application of terminal decrement and requested edits to inputs, including removal of PAS for comparators (i.e. revised base case without comparator PAS included)*

Outcome	IsaPd	Pd	PanVd
Totals, discounted			
Costs (£)	[redacted]	[redacted]	[redacted]
LYs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Difference (IsaPd) vs. Comparator			
Costs (£)		127,267	184,053
LYs		1.649	1.144
QALYs		1.071	0.849
ICER (IsaPd) vs. Comparator			
Cost (£) per life-year saved		77,193	160,842
Cost (£) per QALY saved		118,816	216,856
* includes PAS for Isa ([redacted]) only			

Table 14: PSA for revised base case without comparator PAS included*

Outcome	IsaPd	Pd	PanVd
Totals, discounted			
Costs (£)	[redacted]	[redacted]	[redacted]
LYs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Difference (IsaPd) vs. Comparator			
Costs (£)		137,519	196,393
LYs		1.628	1.056
QALYs		1.055	0.791
ICER (IsaPd) vs. Comparator			
Cost (£) per life-year saved		84,486	185,998
Cost (£) per QALY saved		130,321	248,197
* includes PAS for Isa ([redacted]) only			

Figure 4: Scatter plot of simulations on cost-effectiveness plane, IsaPd vs Pd (revised base case without comparator PAS included)

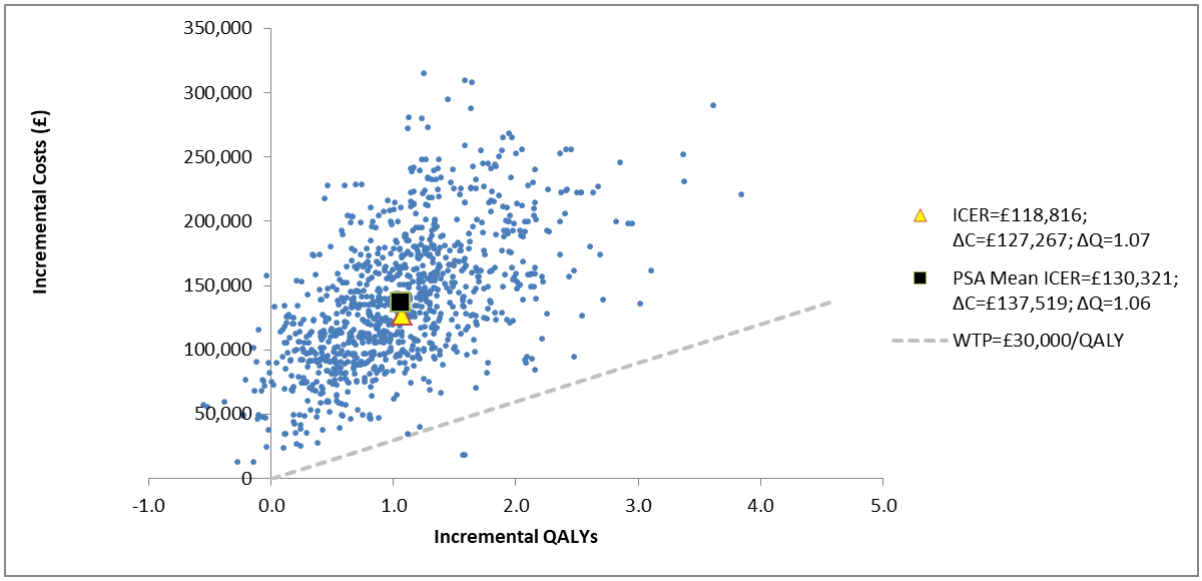


Figure 5: Scatter plot of simulations on cost-effectiveness plane, IsaPd vs PanVd (revised base case without comparator PAS included)

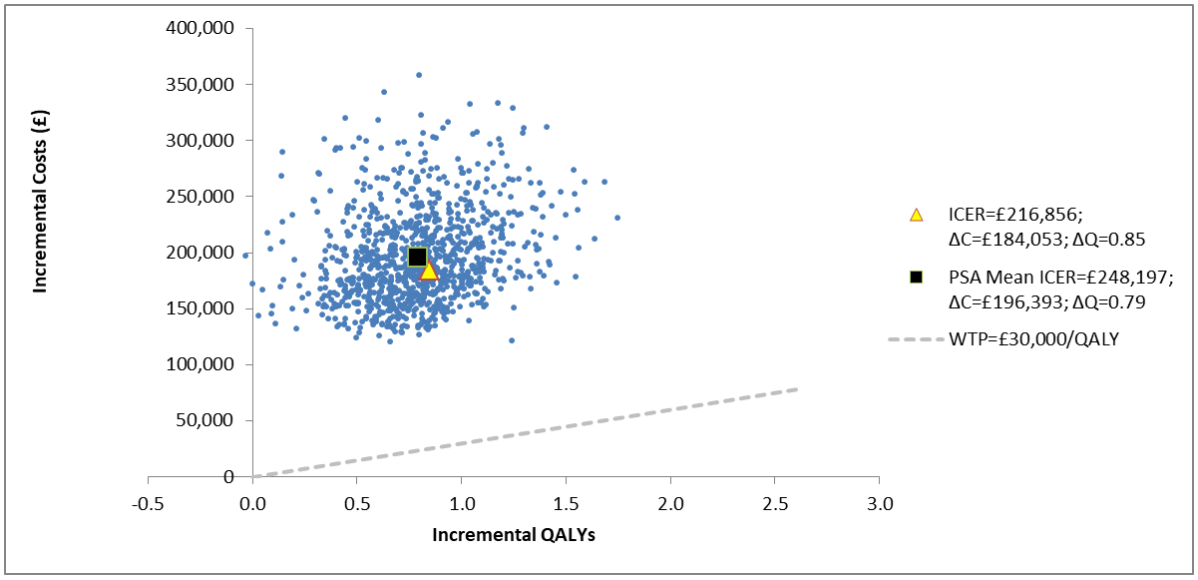
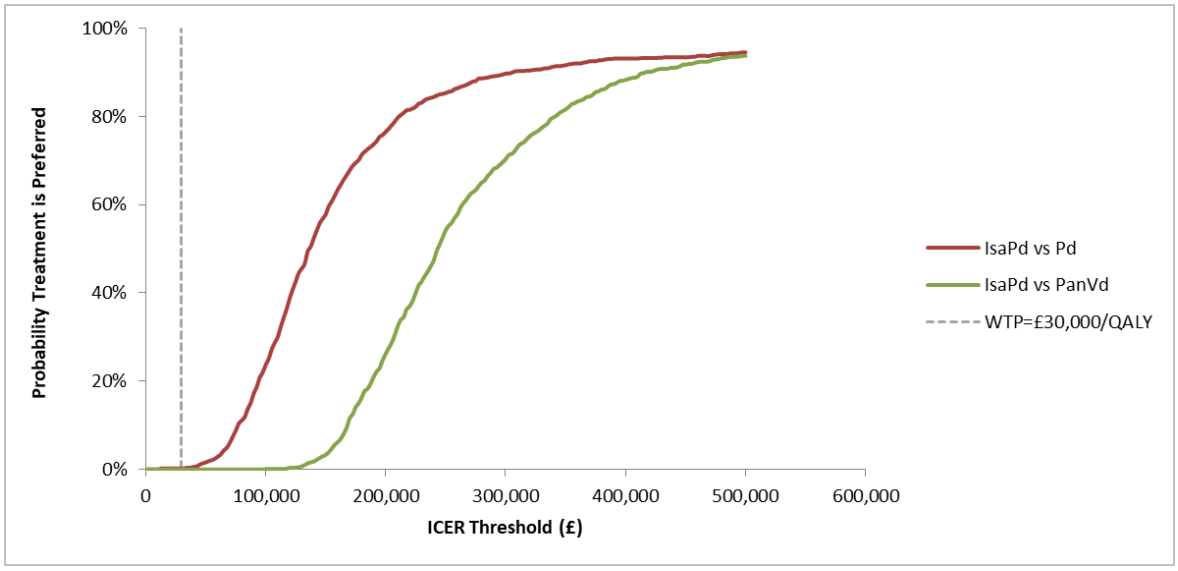


Figure 6: Pairwise CEACs for IsaPd vs Pd and IsaPd vs PanVd (revised base case without comparator PAS included)



B3. Priority. Please provide an ICER using the following assumptions whilst keeping everything else constant: (i) Utility in the PFS and PD health states are assumed independent of whether a patient is on treatment, and (ii) Removing the estimated Mean Duration of Post-Progression Treatment (Months) (Cells D21:E23 in the 'Costs-Other' Worksheet).

Regarding (i), the utility values in the model have been replaced with values estimated using a GEE regression equation in which there is no distinction between assessments when patients were on vs. off therapy. (ii) The mean duration of post-progression treatment has also been set to zero.

B4. Please provide the data sets used to fit the parametric survival functions (TTD, PFS, PFS on Tx and OS) for the two arms.

As mentioned in the clarification call on 9 December, Sanofi requires additional time to address this request. We are currently investigating whether we can release this information to the ERG within the context of patient consent in ICARIA trial.

We are keen to provide the relevant data; however Sanofi has a policy on the sharing of data with researchers that is rigorously adhered to. In order to ensure the data is analysed to the high standards required by the industry in general, a statistical analysis plan must be presented to the company with details of precisely what analyses will be carried out before release of data. In this way we will be able to provide the right data for the requested analysis. Sanofi would also require that the results of the new analyses are provided to the

company for verification prior to further dissemination, for example to stakeholders during the consultation phase.

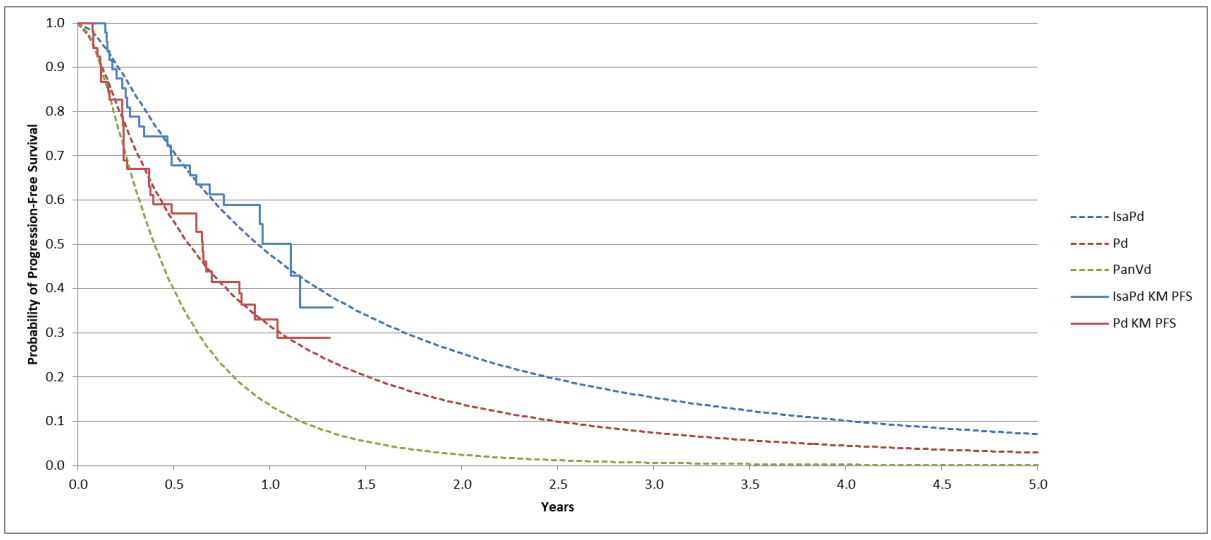
B5. Please clarify whether parameters that should be ordered have been sampled independently. A recent paper details how to ensure the ranking remains constant whilst maintaining the mean and confidence intervals. Ren, Minton, Whyte et al. Pharmacoeconomics 2018 36(3): 341-347.

We recognise that PFS, PFS on-treatment, and OS are ordered outcomes similar to those described in the Ren paper. In particular, PFS on-treatment can be no greater than TTD and PFS and PFS and TTD can be no greater than OS. We ensure the appropriate ordering of mean values for these outcomes based on KM curves (i.e., RMST) in the PSA by sampling from the joint bootstrap distributions derived from the trial data. Bootstrapping ensures that for any given sample the KM of the distributions are appropriately ordered. Because the parametric survival distributions are fit independently to each outcome, there does remain the possibility that the fitted curves are not ordered appropriate across the entire modelling time horizon. The model therefore constrains the distributions to ensure that PFS on-treatment is never greater than TTD and PFS, and TTD and PFS are never greater than OS.

B6. Please clarify why the data (Kaplan-Meier curves for PFS by treatment group in the 4th line population) in Figure 14 do not appear equivalent to those in Figure 37.

Figure 37 in the company submission is incorrect. Please see correct version of the PFS curve (**Figure 7**, below).

Figure 7: Model Projection of PFS on-treatment and KM Estimates of PFS for IsaPd and Pd (lognormal-R)



B7. In the model, the company uses the assumption of a constant death rate over time applied to PFS events (note made by the company in the model, worksheet 'Comp1 Calc', cell DA24). The company states "*PFS events are deaths in the beginning of the model, but decrease over time. This is why PFS events and PPS do not line up*". Please clarify in which basis this assumption was made and to what extent the lack of alignment of between PFS events and PPS affects the results of the analysis.

For simplicity, the model assumes that a constant proportion of PFS events are deaths. Accordingly, the model projects a small proportion of patients will die in the first few weeks of the modelling time horizon. However, the probability of death derived from the OS distribution during this period is zero/small. Accordingly, PPS (based on the difference between OS and PFS) is less than the estimated percent of patients in the PPS state implied by the PFS curve and the (constant) proportion of PFS events that are deaths. This inconsistency of the curves has no material impact on the model results.

B8. Please provide the number of respondents at each treatment cycle and at the end of the trial in Tables 24 and 25. Please provide an explanation for the much higher change from baseline in the IsaPD arm than the PD arm and whether covariates were considered in this analysis?

Revised tables for both EQ-5D-5L health-state utility values (HSUV) and visual analogue scale (VAS) are provided below with the number of respondents at each treatment cycle and at the end of treatment (Table 15 and Table 16).

Table 15: ICARIA-MM key secondary endpoint – EQ-5D-5L HSUV, 4L (safety population†)

	Pd (N=53)			IsaPd (N=49)		
	Mean (SD)†	CFB	Number of observations	Mean (SD)†	CFB	Number of observations
Baseline	0.66 (0.25)	—	53	0.74 (0.20)	—	48
Treatment cycle 2‡	0.71 (0.25)	0.04 (0.24)	48	0.74 (0.25)	0.00 (0.20)	44
Treatment cycle 3‡	0.73 (0.21)	0.02 (0.19)	42	0.73 (0.25)	–0.00 (0.20)	45
Treatment cycle 4‡	0.74 (0.25)	0.05 (0.27)	40	0.78 (0.22)	0.04 (0.19)	43
Treatment cycle 5‡	0.70 (0.20)	0.02 (0.24)	34	0.78 (0.24)	0.05 (0.19)	38
Treatment cycle 6‡	0.74 (0.25)	0.05 (0.23)	27	0.77 (0.17)	0.01 (0.14)	36
Treatment cycle 7‡	0.69 (0.25)	0.01 (0.29)	28	0.75 (0.20)	–0.00 (0.16)	35
Treatment cycle 8‡	0.71 (0.26)	0.00 (0.28)	25	0.74 (0.27)	–0.01 (0.24)	33
Treatment cycle 9‡	0.68 (0.34)	–0.04 (0.35)	23	0.76 (0.16)	0.01 (0.13)	28

	Pd (N=53)			IsaPd (N=49)		
Treatment cycle 10‡	0.68 (0.26)	–0.03 (0.27)	21	0.81 (0.15)	0.05 (0.17)	28
Treatment cycle 11‡	0.66 (0.18)	–0.04 (0.27)	19	0.75 (0.17)	0.01 (0.15)	26
Treatment cycle 12‡	0.72 (0.19)	–0.01 (0.25)	17	0.76 (0.19)	0.01 (0.12)	21
Treatment cycle 13‡	0.72 (0.23)	0.01 (0.25)	15	0.77 (0.15)	0.02 (0.12)	18
Treatment cycle 14‡	0.73 (0.23)	0.06 (0.28)	11	0.80 (0.14)	0.07 (0.14)	13
EOT§	0.58 (0.33)	–0.12 (0.32)	26	0.43 (0.29)	–0.28 (0.19)	17

†A higher score represents a better level of quality of life.
‡At Day 1. §EOT: 30 days after last study treatment administration.
Abbreviations: CFB, change from baseline; EQ-5D-5L, Euro QoL Group self-report questionnaire with 5 dimensions and 5 levels per dimension; EOT, end-of-treatment; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; MM, multiple myeloma; Pd, pomalidomide, low-dose dexamethasone; SD, standard deviation.

Table 16: ICARIA-MM key secondary endpoint – Visual analogue scale – EQ-5D-5L, 4L population

	Pd (N=53)			IsaPd (N=49)		
	Observed score† Mean (SD)	CFB	Number of observations	Observed score†	CFB	Number of observations
Baseline	64.17 (19.66)	—	53	68.46 (19.96)	—	48
Treatment cycle 2§	65.35 (19.45)	0.96 (18.80)	48	66.64 (19.38)	–1.18 (19.64)	44
Treatment cycle 3§	69.07 (16.99)	1.90 (19.00)	42	69.84 (20.77)	1.44 (20.17)	45
Treatment cycle 4‡	69.08 (16.31)	2.93 (18.95)	40	70.56 (18.61)	2.07 (18.67)	43
Treatment cycle 5‡	69.68 (17.21)	4.74 (18.20)	34	71.39 (14.64)	2.18 (19.26)	38
Treatment cycle 6‡	68.63 (17.84)	3.22 (17.37)	27	72.36 (14.23)	2.06 (17.47)	36
Treatment cycle 7‡	67.00 (16.73)	3.25 (19.72)	28	76.20 (13.00)	4.40 (16.97)	35
Treatment cycle 8‡	67.76 (16.23)	0.76 (22.35)	25	71.03 (18.31)	0.36 (18.67)	33
Treatment cycle 9‡	68.87 (18.92)	0.17 (22.51)	23	72.57 (15.38)	0.50 (14.32)	28
Treatment cycle 10‡	67.29 (16.49)	–0.38 (20.73)	21	73.21 (14.81)	–1.32 (14.35)	28
Treatment cycle 11‡	67.26 (16.74)	1.00 (23.04)	19	74.12 (13.74)	2.08 (15.76)	26
Treatment cycle 12‡	70.06 (14.34)	1.88 (23.62)	17	70.76 (14.13)	–3.14 (13.60)	21
Treatment cycle 13‡	70.07 (12.33)	4.40 (21.50)	15	70.11 (14.64)	–2.39 (15.49)	18

	Pd (N=53)			IsaPd (N=49)		
Treatment cycle 14‡	71.73 (15.99)	6.36 (23.59)	11	75.77 (14.37)	2.92 (15.59)	13
End-of-treatment§	58.50 (20.19)	–5.81 (20.63)	26	50.12 (21.68)	–11.00 (21.32)	17

†Safety population evaluable for quality of life assessment: patients from the safety population who have completed the baseline and at least 1 post baseline assessment.
‡A higher score represents a better level of quality of life.
§End-of-treatment: 30 days after last study treatment administration.
Abbreviations: CFB, change from baseline; EQ-5D-5L, Euro QoL Group self-report questionnaire with 5 dimensions and 5 levels per dimension; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; MM, multiple myeloma; Pd, pomalidomide, low-dose dexamethasone; SD, standard deviation.

In response to the second part of this question, the results above are descriptive statistics so there are no adjustments or stratification. This means there are no covariates included in the analysis. For a negative change from baseline (HSUV or VAS), a higher change means a higher deterioration. So, the results suggested lower deterioration for Pd arm than IsaPd arm at some of the time points e.g. Cycle 10, while greater improvement for IsaPd than Pd e.g. Cycles 7, 9, and 11. (Note that end-of-treatment (EOT) visit is not at the same cycle for everybody as this is 30 days after last study treatment administration).

B9. Can the company provide an explanation for the low value for the utility of the PFS off-treatment state in the IsaPD arm, which is lower than for the PPS off treatment state (Tables 40 and 44)?

This was indeed an unexpected result and we can only speculate why the utility value for PFS off-treatment is less than that for PPS off-treatment. It is possible that patients discontinue treatment before progression due to AEs and the lower utility during this time is reflective of the effects of AEs. This also may be spurious finding reflecting the small numbers of EQ-5D assessment in the PFS off-treatment health state (Table 17).

Table 17: EQ-5D assessments in the PFS-off treatment health state

Time	Number of patients	Number of observations
Baseline	50	50
IsaPd Pre On	47	394
IsaPd Pre Off	7	8
IsaPd Post	19	60
IsaPd Post On	16	46
IsaPd Post Off	12	14
Near_Death84	7	17
Baseline	56	56
Pd Pre On	46	328
Pd Pre Off	7	9
Pd Post	25	75
Pd Post On	20	42
Pd Post Off	21	33
Near_Death84	12	20
90 Post	44	135
91 Near_Death84	19	37

During the model validation process, we sought KOL opinion on whether this difference might be possible in clinical practice. According to the KOLs, a lower utility on PFS-off treatment is not unusual as this may reflect experience of serious adverse events that means the patients discontinue treatment. So utility is worse because patient has experienced a serious adverse event and they have to stop their experimental treatment. In 4L setting, where patients are at the end of line in terms of treatment option, having to stop a new experimental treatment that may have improved their survival, could have a bigger impact on quality of life. While a lower utility might be expected for PFS off-treatment, the clinicians did highlight that patients who have progressed will have lower QoL than PFS off-

treatment and progressed off-treatment should have lowest QoL. One KOL noted that some patients in post-progression on-treatment could have a higher QoL than patients in PFS off-treatment – although this depends on whether patients respond to treatment (i.e. higher QoL if respond to next treatment however only about 40% of patients will respond to the post-progression treatment; other 60% have poorer QoL), whether patients have progressed enough to discontinue their post-progression treatment or as well as the impact of the post-progression treatment on their response status. However, in general, the KOLs were clear that the ICARIA-MM results in this respect were an anomaly as it is not reasonable to expect palliative patients (i.e. in the PPS state) to have higher quality of life than progression-free state. Finally, one KOL said it seems implausible that QoL is the same across the treatment arms in PPS off-Treatment, as QoL will depend on the subsequent treatment (e.g. higher QoL if patients receive subsequent Dara vs lower if patients receive PanVd or chemotherapy). Based on the EQ-5D-3L utility in ICARIA-MM, feedback from the KOL would suggest that IsaPd utility values were conservative. Therefore, we tested in SA the impact of using the EQ-5D-5L utilities instead, and the ICER reduced to £115,658 (Includes all ERG preferred changes, model fixes and NO comparator discounts. Isa discount = [redacted]).

B10. Please clarify if collecting EQ-5D at the start of each cycle would potentially overestimate utility, as any adverse reaction to the treatment would not be recorded.

Because patients are likely to experience AEs during/shortly after receipt of medications, it is certainly possible that utility values collected at the beginning of each cycle, prior to the receipt of medications may yield overestimates of average utility values, to the extent that there is a gap between the last receipt of treatment in one cycle and the first receipt of treatment in the next cycle. The gap between last dose of Isa in prior cycle and first dose of next cycle is 7 days in cycle 1 and 14 days in subsequent cycles. The extent to which this might bias comparisons is not estimable, lacking information on utility values in between cycles.

There is also is no optimum time to collect EQ-5D, but it is typical to collect this data at the start of treatment cycle. In ICARIA-MM trial, EQ-5D were administered on day 1 of each cycle (i.e. every 2 weeks) therefore it is reasonable to assume that serious adverse reactions are likely to be captured in the subsequent EQ-5D questionnaire completed by the patient.

B11. Please clarify how many patients carried on subsequent therapy treatment after progression in each arm in ICARIA-MM and the duration for each treatment.

Please see Table 55 in the company submission for the list of subsequent therapies used in the model and Table 57 for the duration for each.

B12. In CS (pages 142 and 143, and Table 57), the company states that the average duration of treatment for subsequent treatments for MM was estimated using data from a Kantar Health Study of treatments in RRMM in Western Europe. Please clarify why external data was used for estimating the average duration of treatment, when the proportion of patients receiving the top ten subsequent anti-cancer treatments were estimated based on data from ICARIA-MM trial?

Although data on the utilisation of subsequent therapies was recorded in the ICARIA-MM trial, these data were not analysed for duration of therapy. This was due to a number of limitations including limited numbers of patients receiving specific treatments of interest, lack of information on how specific treatments were received in combination with other specific treatments (i.e., as treatment regimens) and uncertainty regarding the accuracy of coding with respect to discontinuation of treatment, required for estimation of duration of therapy under conditions of censoring.

B13. Clarify how generalisable the treatments in Table 56 are to England. If there are key differences, qualitatively provide an indication on the impact on the ICER.

According to KOL opinion, there were some differences in the post study treatments in ICARIA-MM vs UK clinical practice (see Table 18 below). These differences have been tested in the SA. The resultant ICER was £128,798 (with only PAS discount on isatuximab, a slight increase over the base case (with PAS assumptions).

Table 18: Post-progression treatments in the UK (clinical expert feedback)

Post-progression therapy	Proportion of patients, by treatment regimen (%)											
	IsaPd			Pd			PanVd			Dara		
	KOL 1	KOL 2	KOL 3	KOL 1	KOL 2	KOL 3	KOL 1	KOL 2	KOL 3	KOL 1	KOL 2	KOL 3
Bendamustine	14.94%	10%	15%	8.77%	10%	10%	10.00%	10%	20%	0.00%	10%	10%
Bortezomib	20.69%	30-40%	20%	18.42%	30-40%	20%	15.00%	0%	0%	0.00%	30-40%	0%
Carfilzomib	0.0%	<5%	0%	0.0%	<5%	0%	0.00%	<5%	0%	0.00%	<5%	0%
Daratumumab	0%	0%	0%	0%	10-15%	40%‡	0.00%	10-15%	30%‡	0.00%	0%	0%
Etoposide	6.90%	<5%	0%	1.75%	<5%	0%	0.00%	<5%	0%	11.00%	<5%	0%
Ixazomib	0.00%	0%	0%	0.0%	0%	0%	0.00%	0%	0%	0.00%	0%	0%
Lenalidomide	0.0%	0%	0%	0.0%	0%	0%	0.00%	0%	0%	0.00%	0%	0%
Melphalan	10.34%	5%	20%	3.51%	5%	20%	0.00%	5%	10%	17.00%	5%	10%
Panobinostat	3.45%	30%	20%	1.75%	30%	20%	0.00%	0%	0%	0.00%	30%	0%
Pomalidomide	0.0%	0%	0%	0.0%	0%	0%	0.00%	60-70%	25%	0.00%	30-40%	80%
Thalidomide	-	20%	-	-	20%	-	-	20%	-	-	20%	-
Cyclophosphamide	-†	20%	-	-†	20%	-	-†	20%	-	-†	20%	-
Dexamethasone	-†	20%	-	-†	20%	-	-†	20%	-	-†	20%	-

Abbreviations: Dara, daratumumab; IsaPd, isatuximab, pomalidomide and low-dose dexamethasone; KOL, key opinion leader; PanVd, panobinostat, bortezomib and low-dose dexamethasone; Pd, pomalidomide plus low-dose dexamethasone.

† Mentioned as a treatment option by KOL, but no value provided; ‡ Dara only used as 4th line therapy – if Pd given 4th line, then only very small proportion would get Dara as subsequent therapy.

Black text indicates the values provided by the KOLs are different to those presented in the discussion guide; Light green text indicates values presented in the discussion guide were considered reasonable by the KOL; Dark green text indicates the value presented in the discussion guide was not explicitly validated by the KOL (i.e. the KOL did not comment on the value specifically).

B14. Please clarify the calculations within cell FB29 in worksheets 'Comp1 Calc', 'Comp2 Calc' and 'Comp3 Calc'. Can the company explain why:

(i) The utilities are applied as being 'one-off' (applied to the sum of patients in Post-Progression On-Therapy in the whole time horizon);

(ii) the value used is the difference between the utilities for PFS on Tx and PFS off Tx. The company states in pages 96 and 97 that *""one-off" incremental QALYs assigned at the point of progression to reflect any incremental effects of treatment post-progression*",

(i) The decrements in QALYs associated with being on therapy in the post-progression state are applied as a one-off as this simplification avoids explicitly tracking patient residency in post-progression on-therapy by model cycle.

(ii) We assume there is an error in the question and instead should be PPS on-treatment and PPS off-treatment. The one-off QALY applied in each cycle represents the incremental QALY associated with being on- vs. off-therapy in the progression state and is calculated as the difference in utility for PPS on therapy and PPS off therapy times the mean duration of post-progression therapy (for those who progress while on therapy). This approach is employed because there is no explicit accounting of state membership in the PPS On- vs. Off-therapy states. The On-treatment QALYs in cell FB29 can therefore be interpreted as the change in QALYs as a result of being On-therapy vs. Off-therapy.

B15. Please clarify the calculations within cells FD29:FD1072 in worksheets 'Comp1 Calc', 'Comp2 Calc' and 'Comp3 Calc'. Please explain why the utilities for PPS off Tx are being applied indefinitely to all patients who progress (column DH, Post-progression cumulative).

This column calculates the PPS off treatment QALYs, which equal the probability of residing in the state times the health state utility (adjusted for general population utility as a ceiling if selected) minus the one-off decrement associated with the "terminal" period. The latter is calculated as sum of the absolute incremental probability of death during the 12-week cycle beginning with the current cycle (i.e., the "SUM(DK29:INDEX(DK29:DK1072,util.term_duration))" term in cell FD29) times the decrement in utility during the terminal period (e.g., comp1.term_util), times the number of years per cycle (*7/days_per_year). This calculation reflects the fact that as of any given cycle, the proportion of patients in the terminal period (among those entering the model) can be calculated as the sum of the absolute probability of dying in the next 12 cycles.

B16. Please clarify why the company applies the terminal decrement in two different columns in the model to account for the end of life (terminal) decrements in utility in the model. It is unclear if this represents double counting. The decrement is applied in:

(i) Cells FA29:FA1072, applied as an addition to PFS off treatment QALYs (to the patients who left PFS and died (=PFS events – non-death PFS events) in each cycle;

(ii) Cells FD29:FD1072, applied as a subtraction to PPS off treatment QALYs applied to the patients who die in the current and following 11 cycles ('death (marginal)'), to which is applied the mean treatment decrement duration.

The terminal decrement should only be applied to patients who die. The model is double counting the terminal decrement for those patients for whom death occurred before progression. The updated model has eliminated this error. The change does not have any material impact on the results. We thank the ERG for pointing out this discrepancy.

B17. CS (document B, page 129). Please clarify how the period of utility decrement for terminal decline (12 weeks) was estimated.

The 12 week period over which the utility decrement was estimated was based on published literature suggesting a decline in quality of life during the last 3-6 months prior to death in cancer patients as well as a review of the data from ICARIA-MM to ascertain the duration that would include sufficient numbers of assessments during the terminal period to allow robust estimation of the decrement in utility for the terminal period (5,6).

B18. Please clarify why only the highest administration costs are applied where there are multiple treatments being administered for IsaPD and PD.

This assumption is based on input from NHS pharmacist who said that only a single admin cost would be charged per visit and an approach of applying administration cost to each treatment would be over-counting.

B19. In relation to other costs related to granulocyte colony stimulating factor (GCSF), red blood cell (RBC) and platelets transfusions, please clarify:

(i) why the estimates of the proportions of patients in the Pd arm receiving these interventions and the mean number of each intervention received by patient were obtained from external data (economic model in the manufacturer's submission to NICE for Pd)

(ii) to which extent these estimates reflect current practice for patients receiving 4th line of treatment;

(iii) the sources used to estimate the proportion of patients that have GCSF, RBC transfusions and platelet transfusions worksheet 'Costs_Other", cells G159:I162.

In the original model, the mean number of units for GCSF, RBC transfusions and platelet transfusions per patient for patients receiving Pd, the proportions of patients receiving concomitant treatments were from the economic model in the manufacturer's submission to NICE for the STA of Pd (TA427). For patients receiving IsaPd, the use of these treatments was assumed to be the same as that for Pd (Table 19).

In our revised model submitted at this stage, we have used the data from ICARIA and the expected costs of subsequent treatments were assigned as a one-off cost at therapy initiation. We realise we should have implemented this in the original model but as can be seen from the results, the change in source for granulocyte colony stimulating factor (GCSF), red blood cell (RBC) and platelets transfusion has made marginal difference (Table 20).

In terms of the extent to which the usage of GCSF, RBC and platelets transfusion reflect clinical practice, we were unable to find published data reflecting the use of these treatments in practice. However, we compared the usage to that used in other HTA submissions in fourth line setting (TA427 and TA510).

Table 19: Original model based on published Pd data

	Number of administrations	IsaPd	Pd	PanVd
GCSF	1	0.43	0.43	0.2
RBC transfusion	3	0.49	0.49	0.2
Platelet transfusion	4.79	0.2	0.2	0.2

Table 20: Revised model based on 4L data in ICARIA-MM

	IsaPd		Pd		PanVd	
	No of units	N (%)	No of units	N (%)	No of units	N (%)
GCSF	4.3	36 (70.6)	4.2	29 (50)	1	0.2
RBC transfusion	1.8	11 (21.6)	2.8	24 (41.4)	3	0.2
Platelet	2.3	6 (11.8)	2.4	8 (13.8)	4.79	0.2

transfusion						

B20. Please clarify the calculations and assumptions used in the "Other costs - On-Tx PPS, Undiscounted" and "Other costs - Off-Tx PPS, Discounted" corresponding to cells EO27:29 and EP27:1072 on worksheets 'Comp1 Calc', 'Comp2 Calc' and 'Comp3 Calc'. The current methodology results in zero costs for PPS on Tx related to physician visits, blood counts and biochemistry, whilst the costs for PPS off Tx accounts for all patients in PPS state, regardless of being On Tx or not.

The reason the model calculates Other Costs this way is because the model does not individually account for state residency in PPS On-treatment and PPS Off-treatment, but instead only tracks total PPS residency. The value for On-treatment PPS other costs in cells EO27:EO29 should not be interpreted as the sum total of all the "Other Costs" incurred by progressed patients On-treatment, but rather as the difference in costs between patients in the On- and Off-treatment PPS states. As there is no difference in utilisation of "Other Costs" for On- vs Off-treatment in the base case, the value cell EO29 equals zero. To improve clarity, the column has been re-labelled "Incremental Costs for PPS On-Treatment vs PPS Off-Treatment"

B21. Please can the company explain the results in Figure 43, regarding to no change shown in the deterministic sensitivity analysis tornado chart when the relative dose intensity for Pd is reduced, whilst its increase has the greatest impact.

This is due to wastage, and the fact that the base case vials used per dose is <1 before rounding up. Reducing the amount used through the RDI DSA does not have an impact on costs because in both cases the number of vials required is rounded up to the nearest integer. For example, if the base case vials used per dose was 0.90, and the DSA RDI reduced this to 0.75, there would be no change under the wastage assumption as both are rounded up to the next integer, 1. Similarly, when the high RDI is applied, this results in a vials needed per dose slightly greater than 1, which is then rounded up to 2 vials under the wastage assumption. This essentially results in a doubling of costs for the medication.

B22. Provide probabilistic sensitivity analyses for the scenarios termed 'favourable' and 'unfavourable' (Table 63).

Favourable scenarios with PAS discounts for comparators

Below are results of the PSA for the favourable distribution scenario (TTD: Weibull (U), On-Tx PFS: RCS lognormal (R), PFS: RCS Weibull (R), OS: RCS Weibull (R)) with all other changes to the model except for removal of the PAS discounts for the comparators (**Table 21**).

Table 21: PSA Summary Results, Base Case (4L) – Favourable (with PAS discounts for comparators)

Outcome	IsaPd	Pd	PanVd
Totals, discounted			
Costs (£)	[redacted]	[redacted]	[redacted]
LYs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Difference (IsaPd) vs. Comparator			
Costs (£)		98,011	123,097
LYs		2.320	1.333
QALYs		1.489	0.972
ICER (IsaPd) vs. Comparator			
Cost (£) per life-year saved		42,251	92,368
Cost (£) per QALY saved		65,806	126,697

* includes PAS for Isa ([redacted]), Pd ([redacted]), Panobinostat ([redacted]) and daratumumab ([redacted])

Figure 8: Scatter Plot of Simulations on Cost-effectiveness Plane, IsaPd vs Pd

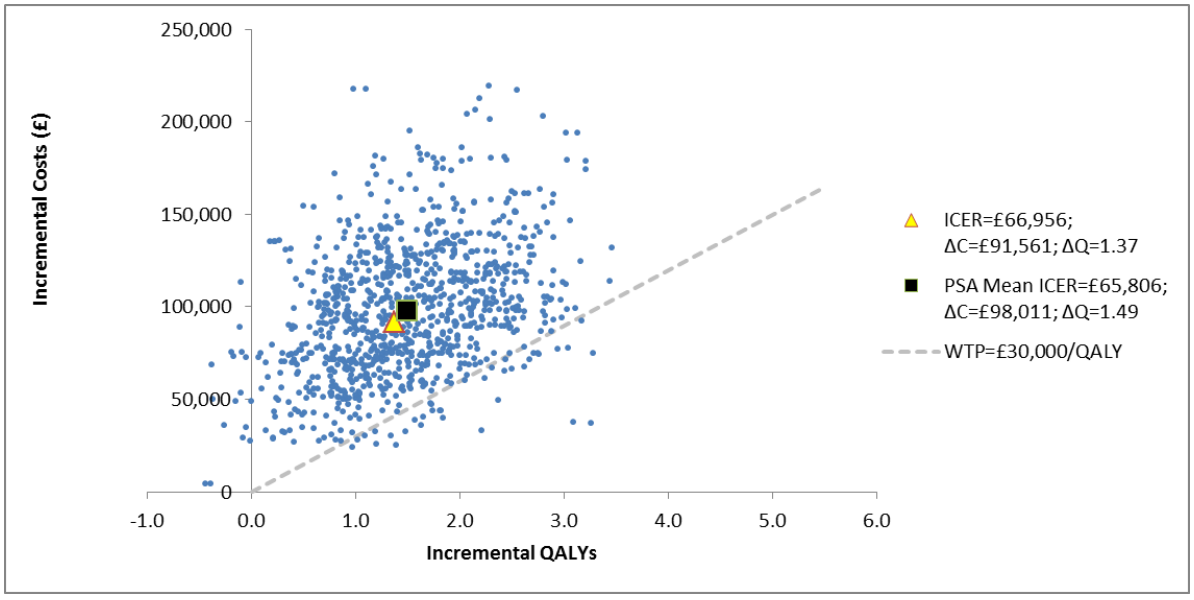


Figure 9: Scatter Plot of Simulations on Cost-effectiveness Plane, IsaPd vs PanVd

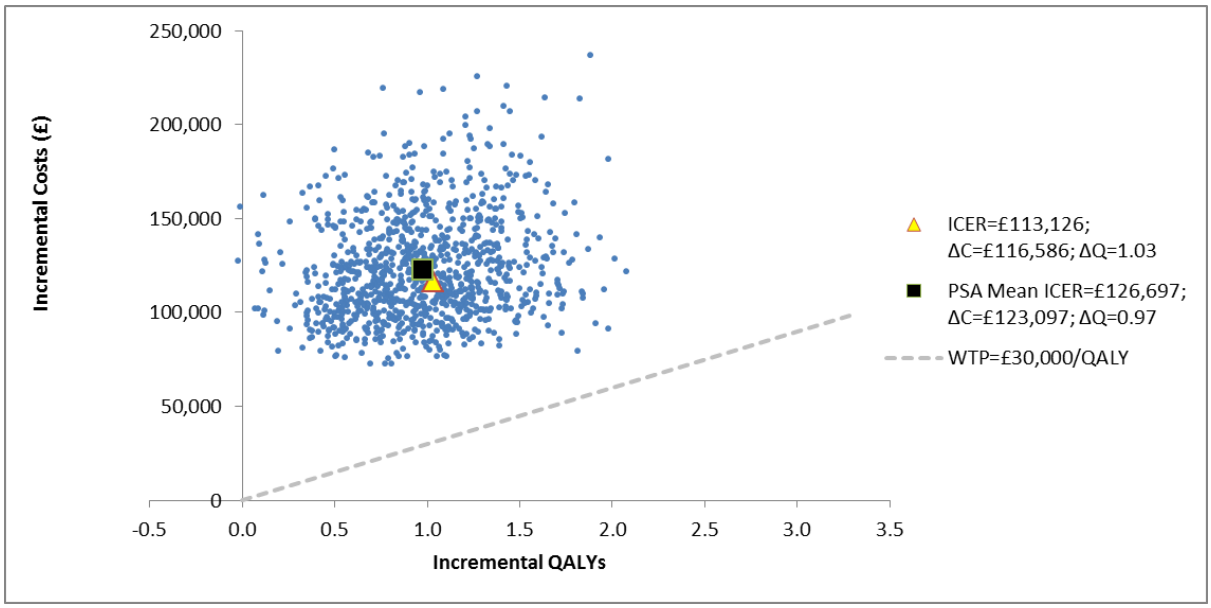
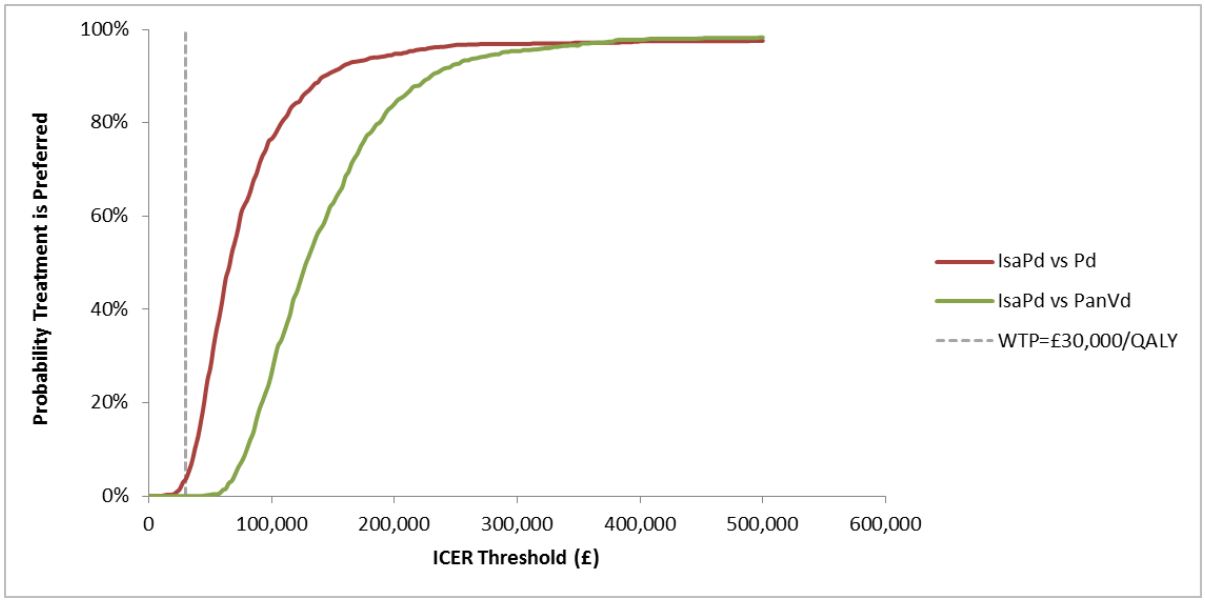


Figure 10: Pairwise CEACs for IsaPd vs Pd and IsaPd vs PanVd



Favourable scenarios without PAS discounts on comparators

Below are results of the PSA for the favourable distribution scenario (TTD: Weibull (U), On-Tx PFS: RCS lognormal (R), PFS: RCS Weibull (R), OS: RCS Weibull (R) with all other changes to the model, including removal of the PAS discounts for the comparators (Table 22).

Table 22: Mean PSA results for favourable scenario (Revised company base case without PAS discount for comparators)

Outcome	IsaPd	Pd	PanVd
Totals, discounted			
Costs (£)	[redacted]	[redacted]	[redacted]
LYs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Difference (IsaPd) vs. Comparator			
Costs (£)		107,464	166,605
LYs		2.320	1.333
QALYs		1.489	0.972
ICER (IsaPd) vs. Comparator			
Cost (£) per life-year saved		46,326	125,015
Cost (£) per QALY saved		72,152	171,478

* includes PAS for Isa ([redacted]) only

Figure 11: Scatter Plot of Simulations on Cost-effectiveness Plane, IsaPd vs Pd

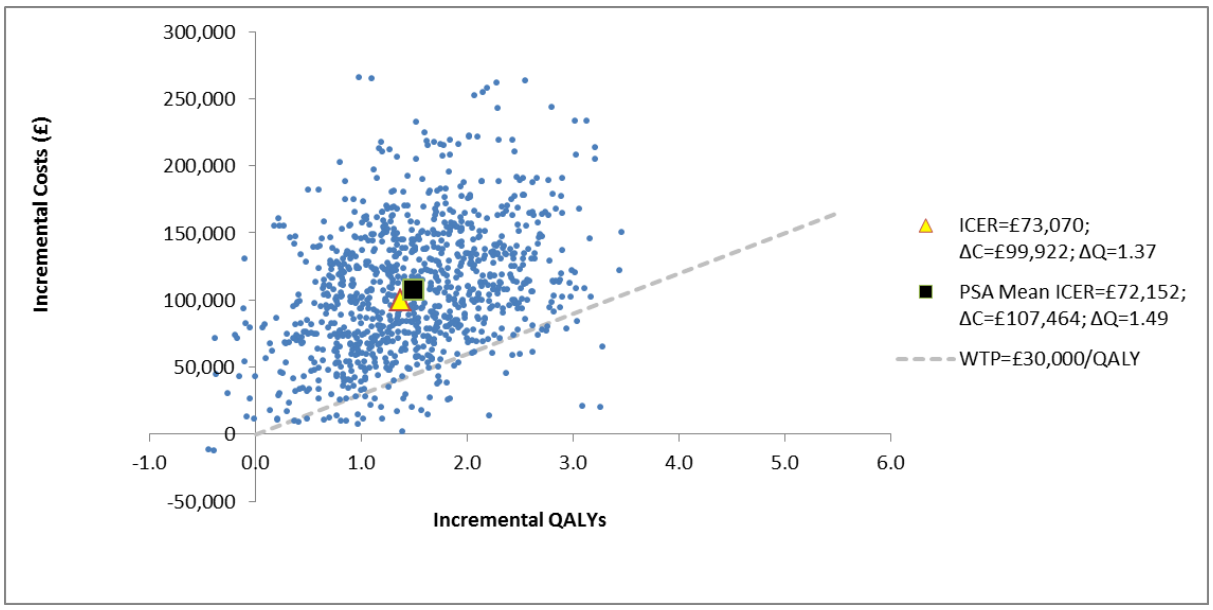


Figure 12: Scatter Plot of Simulations on Cost-effectiveness Plane, IsaPd vs PanVd

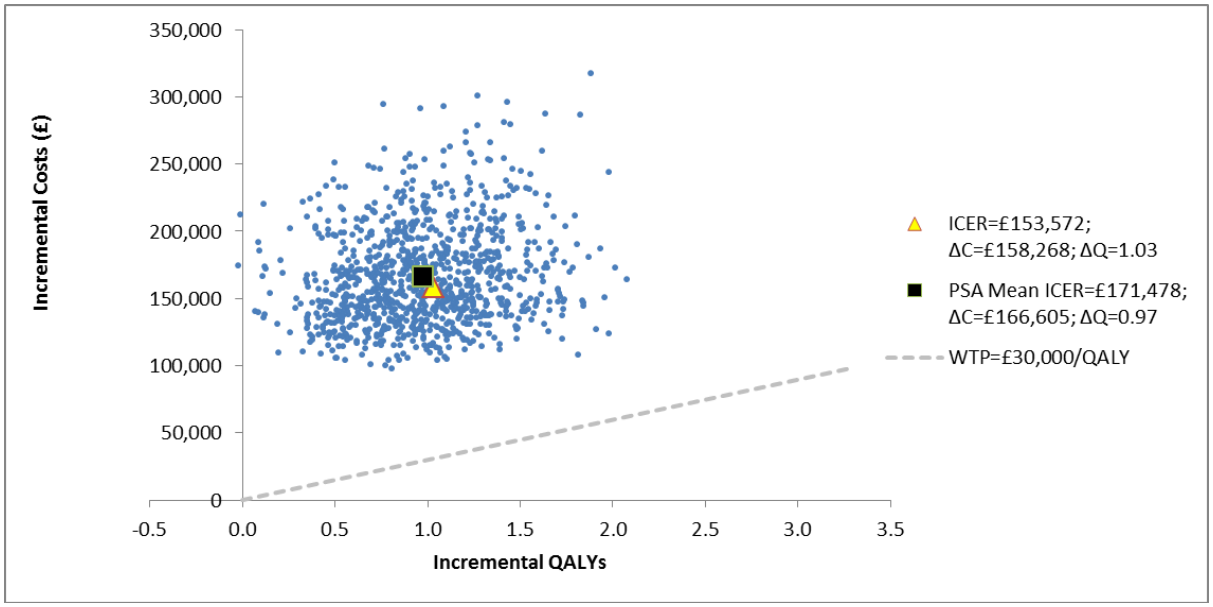
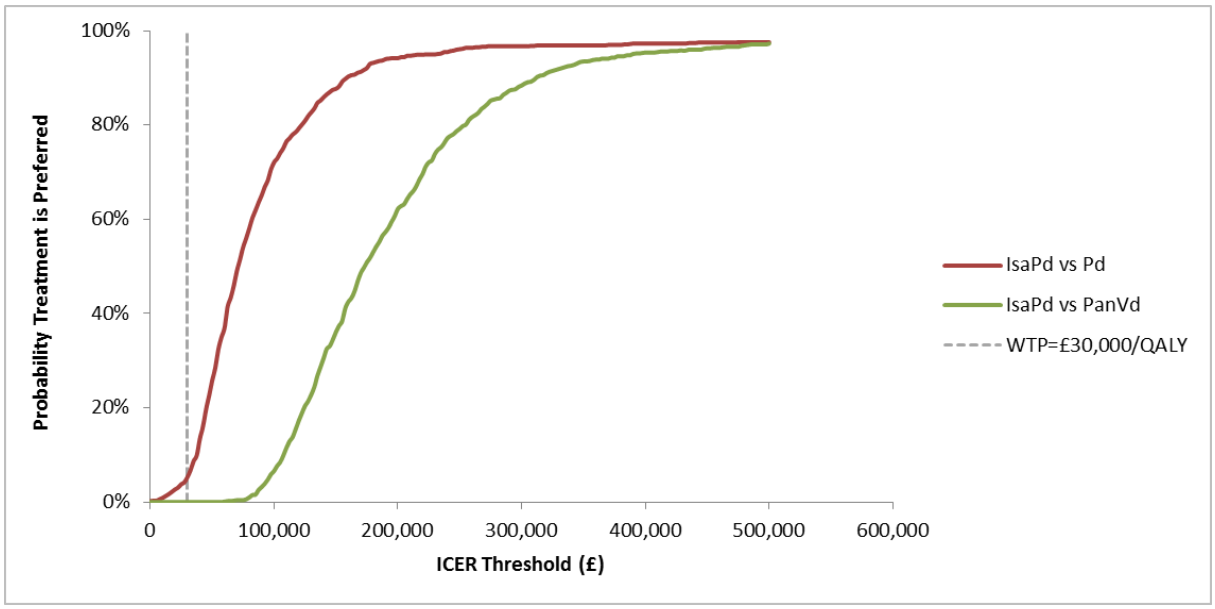


Figure 13: Pairwise CEACs for IsaPd vs Pd and IsaPd vs PanVd



Unfavourable scenarios with PAS discounts for comparators

Below are results of the PSA for the unfavourable distribution scenario (TTD: Log-logistic (R), On-treatment PFS: Log-logistic (R), PFS: RCS Lognormal (R), OS: Lognormal (R)) with all other changes to the model, except for removal of PAS discounts for the comparators (Table 23).

Table 23: PSA Summary Results, Base Case (4L) – Unfavourable (with PAS discounts for comparators)

Outcome	IsaPd	Pd	PanVd
Totals, discounted			
Costs (£)	[redacted]	[redacted]	[redacted]
LYs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Difference (IsaPd) vs. Comparator			
Costs (£)		195,302	259,670
LYs		1.589	1.254
QALYs		1.057	0.959
ICER (IsaPd) vs. Comparator			
Cost (£) per life-year saved		122,910	207,084
Cost (£) per QALY saved		184,717	270,781

* includes PAS for Isa ([redacted]), Pd ([redacted]), Panobinostat ([redacted]) and daratumumab ([redacted])

Figure 14: Scatter Plot of Simulations on Cost-effectiveness Plane, IsaPd vs Pd

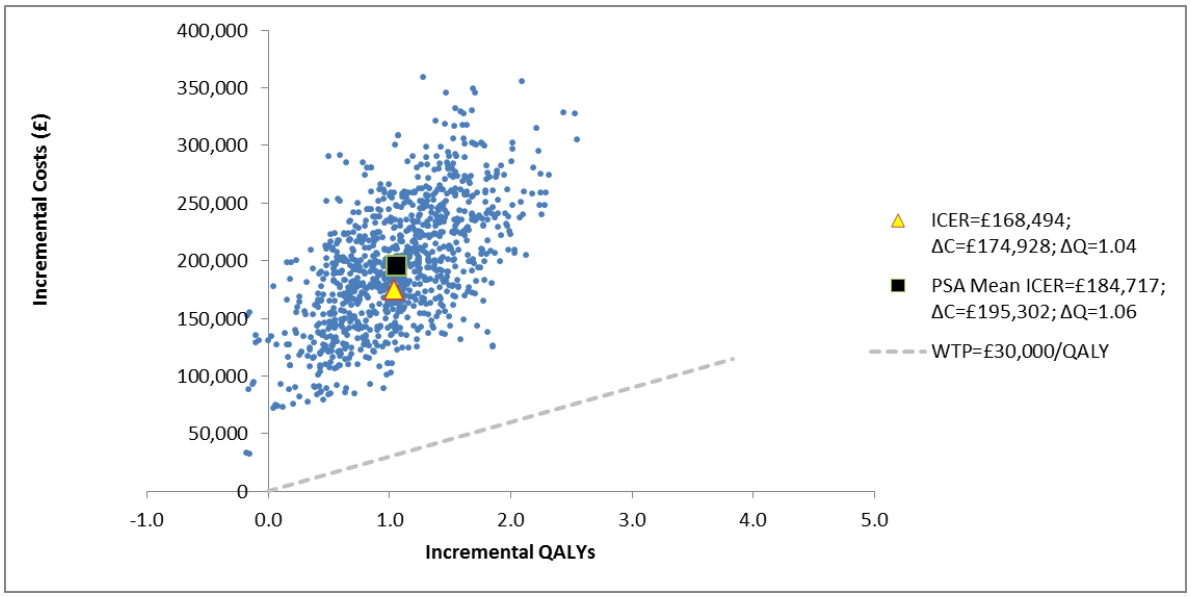


Figure 15: Scatter Plot of Simulations on Cost-effectiveness Plane, IsaPd vs PanVd

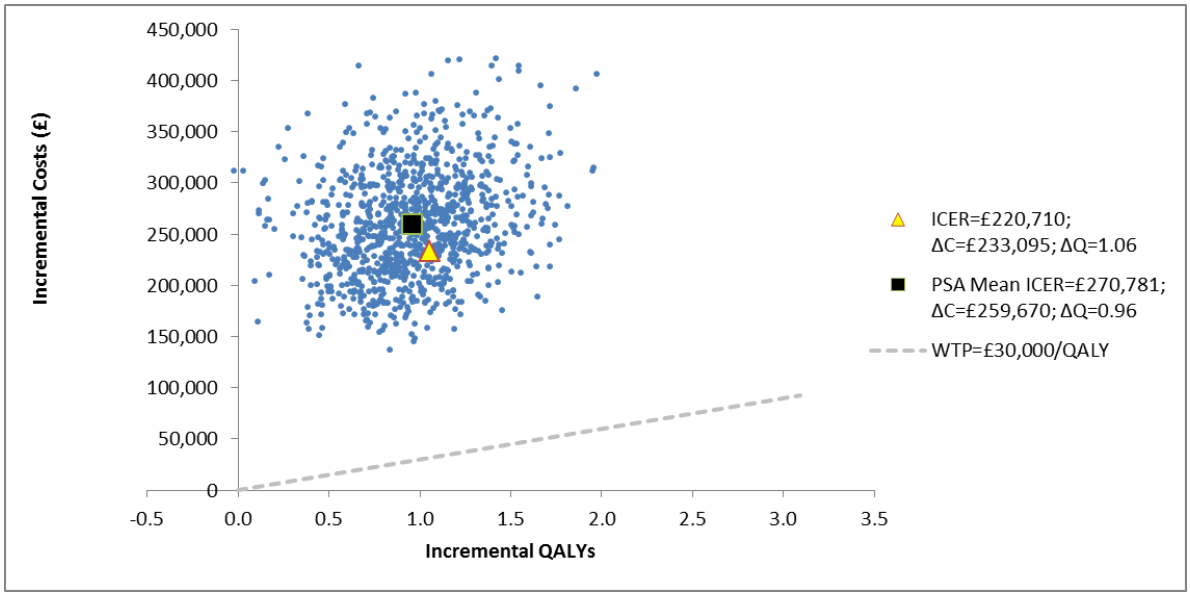
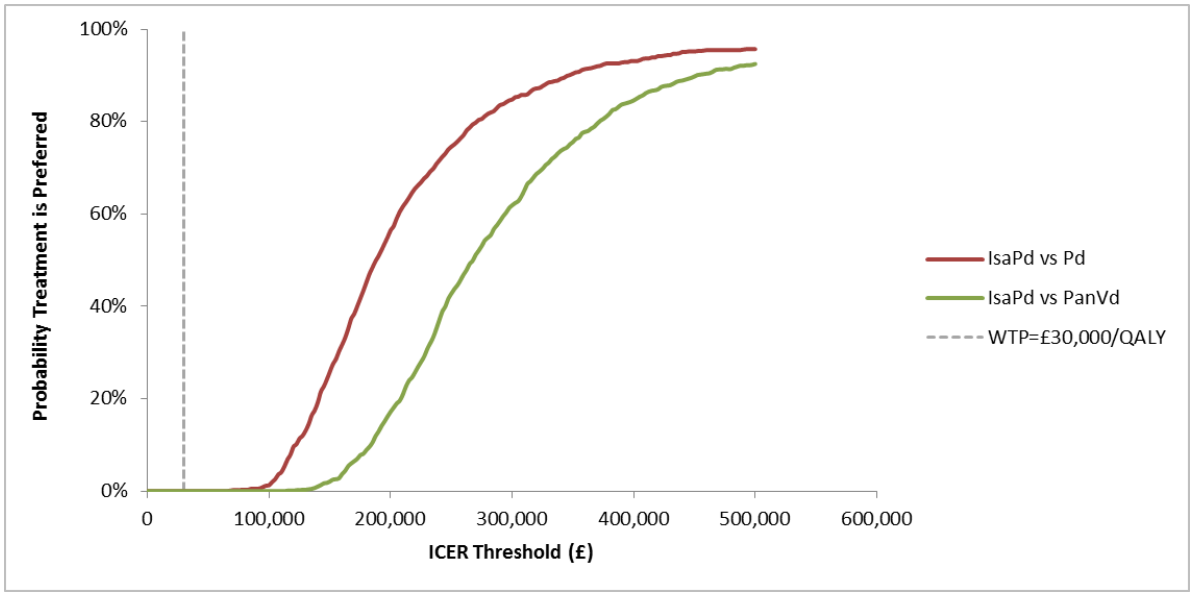


Figure 16: Pairwise CEACs for IsaPd vs Pd and IsaPd vs PanVd



Unfavourable scenarios without PAS discounts for comparators

Below are results of the PSA for the unfavourable distribution scenario (TTD: Log-logistic (R), On-treatment PFS: Log-logistic (R), PFS: RCS Lognormal (R), OS: Lognormal (R)) with all other changes to the model, except for removal of the PAS discounts for the comparators (Table 24).

Table 24. Mean PSA results for unfavourable scenario ((Revised company base case without PAS for comparators)

Outcome	IsaPd	Pd	PanVd
Totals, discounted			
Costs (£)	[redacted]	[redacted]	[redacted]
LYs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Difference (IsaPd) vs. Comparator			
Costs (£)		229,168	347,988
LYs		1.589	1.254
QALYs		1.057	0.959
ICER (IsaPd) vs. Comparator			
Cost (£) per life-year saved		144,223	277,517
Cost (£) per QALY saved		216,747	362,878

* includes PAS for Isa ([redacted]) only

Figure 17: Scatter Plot of Simulations on Cost-effectiveness Plane, IsaPd vs Pd

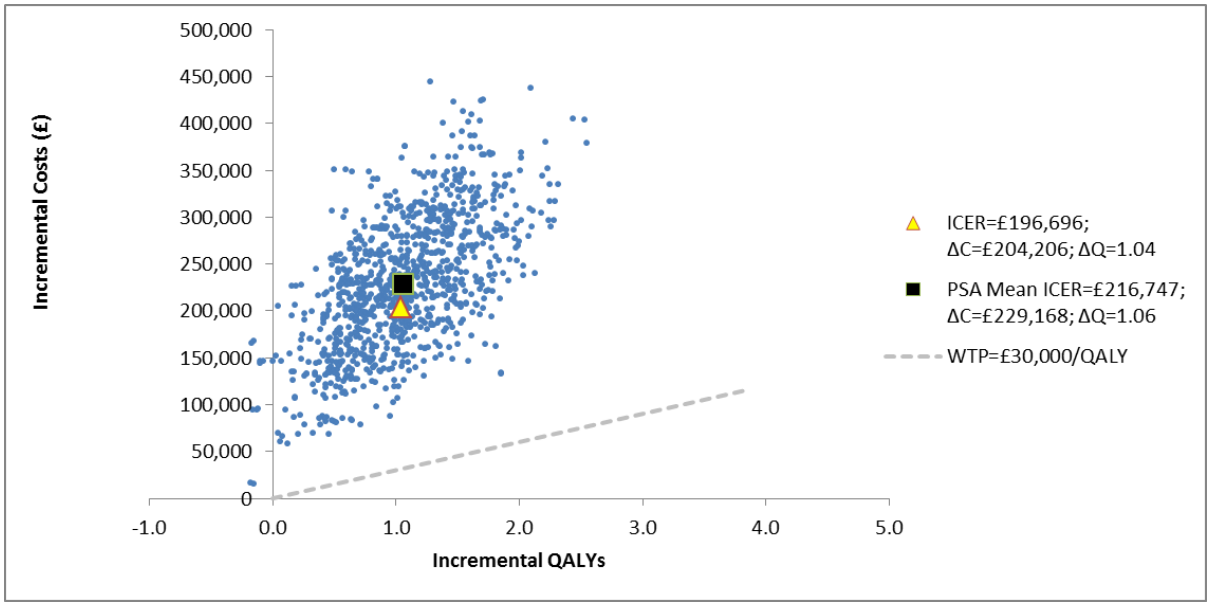


Figure 18: Scatter Plot of Simulations on Cost-effectiveness Plane, IsaPd vs PanVd

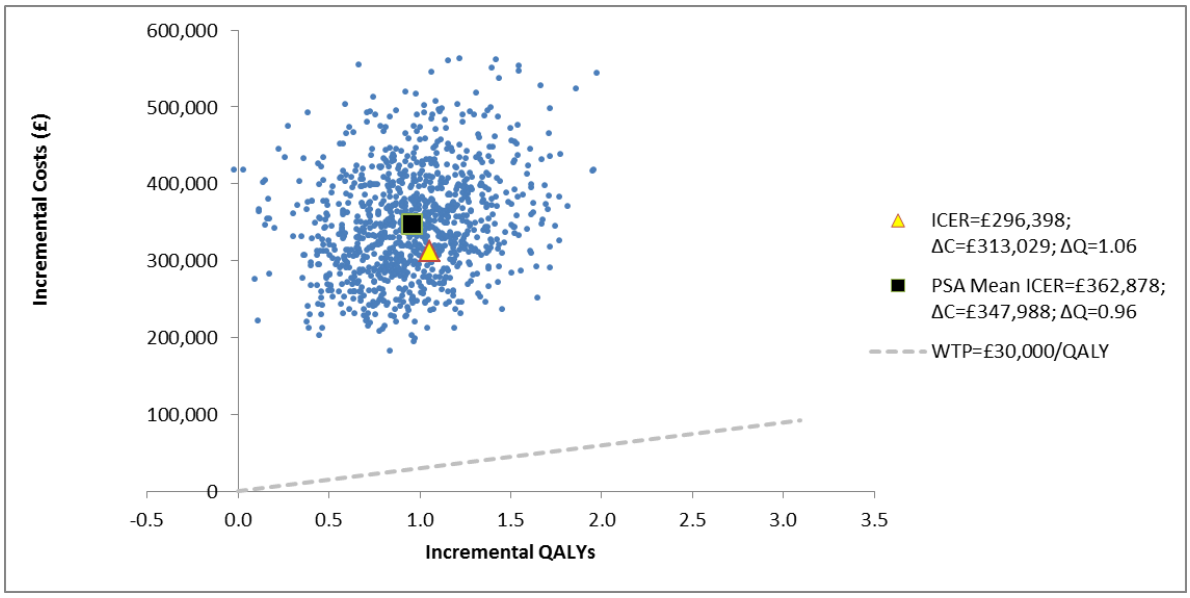
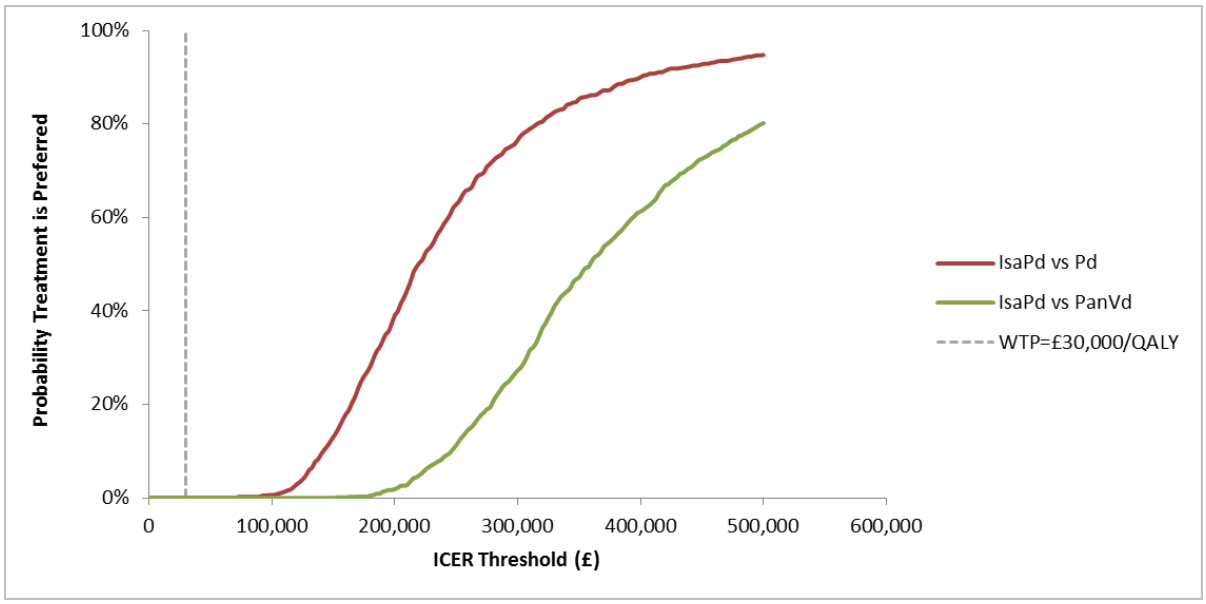


Figure 19: Pairwise CEACs for IsaPd vs Pd and IsaPd vs PanVd



B23. Clarify why it is assumed that for Panobinostat, bortezomib, dexamethasone (PanVD) the utilities are assumed the same as Pd however, the distribution of subsequent treatments is assumed to equal those of IsaPd

The assumption that the use of subsequent therapies for patients receiving PanVd would be the same as that for patients receiving IsaPd was based on the premise that the distribution of subsequent therapies is likely to be most similar for triplet therapies than for triplet and doublet therapies. While it is true that the health state utility values for PanVd were assumed to be the same as PD, the QALYs for the PFS state were adjusted for the decrement in

QALYs reflecting the difference in the incidence of AEs for PanVd versus Pd combined with the disutilities and durations of the AEs. Although Pd was chosen, somewhat arbitrarily, as the "referent treatment" to which the QALY adjustment for AEs was applied, it would also be reasonable to use the health state utility values for IsaPd and apply a decrement in QALYs reflecting the difference in the incidence of AEs for PanVd versus IsaPd.

While the choice of the referent treatment for the utility values is somewhat arbitrary and has little effect on the results, for consistency, we have modified the model so that the health state utilities for PanVd are assumed to be the same as those for IsaPd.

B24. Appendix K (Page 321, Table 57). The company says that "probabilities of AEs for patients receiving PanVd were from the [daratumumab] manufacturer's submission to NICE; values were not specific to 4th line treatment". Please clarify why it was assumed that patients receiving PanVd would have the same probabilities of having AEs as patients being treated with daratumumab, a different type of drug (histone deacetylase inhibitor vs monoclonal antibody that binds to CD38), rather than patients being treated with Isatuximab (also a monoclonal antibody that binds to CD38) or using the Pd data.

Values in model are the numbers reported for PanVd in the Dara NICE submission. Values for the Dara submission were drawn from the PANORAMA-2 trial. Therefore, the adverse events for PanVd are based previously published HTA where assumptions used were not challenged, therefore we chose to use this data for PanVd rather than assumption of same adverse events between IsaPd and PanVd.

B25. Please clarify which utility values were used in the supplementary analysis for IsaPd and PanVd and how they were obtained. The company states that "*As ICARIA-MM does not provide information on utility values for patients receiving PanVd, utility values for this comparator was assumed to be the same as for Pd (Table 55)*". Please clarify if Table 58 presents values for EQ-5D-5L or 3L. Additionally, the values in Table 58 do not match the values used for Pd and IsaPd in Tables 40 (EQ-5D-5L) or (EQ-5D-3L) of document B, nor the values for PanVd in the model. See the table below for a summary of these data.

There is an error in Appendix K, Table 58. The values should be same as that used in the model (Table 24).

Table 25: Comparison of utility value inputs in Appendix K, Table 40 (of company submission) and company model

	Appendix K, Table 58		EQ-5D-5L (Table 40)		EQ-5D-3L (Table 44)		Model		
State	**IsaPd**	**PanVd**	**IsaPd**	**Pd**	**IsaPd**	**Pd**	**IsaPd**	**Pd**	**PanVd**
PFS on treatment	0.719	0.721	0.801	0.781	0.731	0.717	0.731	0.717	0.717
PFS off treatment	0.545	0.544	0.572	0.717	0.473	0.621	0.473	0.621	0.621
PPS on treatment	0.693	0.693	0.724	0.724	0.649	0.649	0.649	0.649	0.649
PPS off treatment	0.584	0.584	0.650	0.650	0.553	0.553	0.553	0.553	0.553
Terminal decrement	-0.134	-0.134	-0.171	-0.171	−0.204	−0.204	−0.204	−0.204	−0.204

B26. Please clarify the reason why the company assumes that the proportion of patients getting GCSF and RBC and platelet transfusions would be the same for patients receiving IsaPd and Pd, while patients receiving PanVd would receive less interventions, based on data available on another STA (Daratumumab).

We agree with the ERG that it is better to use data from the ICARIA-MM trial and we discussed in above under B19. In the revised model, we use the values above from the ICARIA-MM trial for IsaPd and Pd.

We assumed lower values for PanVd based on assumptions made in the Dara STA NICE submission for PanVd. These are lower than that IsaPd in ICARIA because blood-related adverse events (for which GCSF, RBC and platelet transfusion are used) appear to be reported at lower rate for PanVd than IsaPd or Pd.

B27. Please comment on whether the younger age assumed in the model compared with the expected age in clinical practice is likely to influence the ICER. If so, provide an indication on whether this would be favourable or unfavourable to isatuximab.

To do this analysis correctly, one would have to re-estimate the model on subgroups defined on age. As an approximation, we re-ran the model with older ages and found that that change had a minimal impact on outcomes. ICARIA subgroup analyses on PFS show positive treatment effect in all subgroups consistent with the overall treatment effect (including subgroups with poor prognosis), including age. It is notable that the elderly patient

subgroup in ICARIA does demonstrate relatively better outcomes than the younger patients for example in HRQoL.

B28. Please provide an updated estimate of the ICER using annual mortality rates for the general population for years 2016-2018 from Interim Life Tables for England (available since September 2019).

Values have been updated in the model.

B29. Please provide an updated estimate of the ICER using 365.25 days in a year, instead of 365.

Calculations have been updated in the model

B30. CS (document B, page 100). Please clarify whether the infusion costs of diphenhydramine are included in the model. Please, also clarify how the premedication costs for Isatuximab were estimated in the model.

In this model, cetirizine was used in lieu of diphenhydramine as part of the Isa premedication's because costing information for diphenhydramine was not available in either eMIT or BNF. Cetirizine is listed in the SPC as an appropriate equivalent of diphenhydramine. The cost of infusion for cetirizine is assumed to be bundled with the infusion administration cost applied for Isa. In re-computing premedication costs for the purposes of providing the requested clarification, we realized our prior premedication costs were double-counting the costs of dexamethasone. Premedication costs for Isa have been adjusted and were computed as follows (Table 25):

Table 26: Premedication calculations

Medication	Dose	Cost/pack	Units/pack	Mg/unit	Cost/unit	Source
Paracetamol	1000 mg	£2.19	100	500	£0.04	BNF
Ranitidine	50 mg	£1.91	5	50	£ 0.38	eMIT
Cetirizine	50 mg	£0.93	30	10	£0.16	BNF
Total					**£0.58**	
Cycle 1 (Totalx4)					**£2.32**	
Cycle 2+ (Totalx2)					**£1.16**	

Section C: Textual clarification and additional points

C1. In Table 8 (page 42), it looks like there is a number and percentage missing from the cell representing ICARIA-MM patients in 4L on Pd with an ECOG PS of 0. Please can you provide these figures.

The missing values have now been added, please see amended table below (Table 26).

Table 27: Baseline demographics of patients in ICARIA-MM trial (randomised population)

Baseline demographics	ICARIA-MM – ITT population		ICARIA_MM – Patients in 4L	
	Pd (N=153)	IsaPd (N=154)	Pd (N=58)	IsaPd (N=52)
Age, years, mean (SD)	65.2 (9.5)	66.6 (9.1)	64.2 (8.9)	66.1 (8.5)
Age group, years, n (%)				
<65	70 (45.8)	54 (35.1)	27 (46.6)	19 (36.5)
65–74	54 (35.3)	68 (44.2)	22 (37.9)	26 (50.0)
≥75	29 (19.0)	32 (20.8)	9 (15.5)	7 (13.5)
Sex, n (%)				
Male	70 (45.8)	89 (57.8)	27 (46.6)	30 (57.7)
Female	83 (54.2)	65 (42.2)	31 (53.4)	22 (42.3)

Baseline demographics	ICARIA-MM – ITT population		ICARIA_MM – Patients in 4L	
	Pd (N=153)	IsaPd (N=154)	Pd (N=58)	IsaPd (N=52)
Race, n (%)				
White	126 (82.4)	118 (76.6)	51 (87.9)	42 (80.8)
Black or African American	3 (2.0)	1 (0.6)	1 (1.7)	0
Asian	15 (9.8)	21 (13.6)	5 (8.6)	5 (9.6)
Native Hawaiian or other Pacific Islander	1 (0.7)	2 (1.3)	0	2 (3.8)
Missing/Not reported	8 (5.2)	12 (7.8)	1 (1.7)	3 (5.8)
Ethnicity, n (%)				
Hispanic or Latino	3 (2.0)	4 (2.6)	1 (1.7)	3 (5.8)
Not Hispanic or Latino	134 (87.6)	130 (84.4)	51 (87.9)	42 (80.8)
ECOG PS, n (%)				
0	69 (45.1)	55 (35.7)	30 (51.7)	21 (40.4)
1	68 (44.4)	83 (53.9)	23 (39.7)	25 (48.1)
2	16 (10.5)	16 (10.4)	5 (8.6)	6 (11.5)

Baseline demographics	ICARIA-MM – ITT population		ICARIA_MM – Patients in 4L	
	Pd (N=153)	IsaPd (N=154)	Pd (N=58)	IsaPd (N=52)
Geographical region, n (%)				
Western Europe	76 (49.7)	55 (35.7)	29 (50.0)	19 (36.5)
Eastern Europe	20 (13.1)	28 (18.2)	10 (17.2)	13 (25.0)
North America	5 (3.3)	7 (4.5)	0	3 (5.8)
Asia	15 (9.8)	21 (13.6)	5 (8.6)	5 (9.6)
Other countries†	37 (24.2)	43 (27.9)	14 (24.1)	12 (23.1)
Regulatory region, n (%)				
Western countries	97 (63.4)	77 (50.0)	33 (56.9)	27 (51.9)
Other countries‡	56 (36.6)	77 (50.0)	25 (43.1)	25 (48.1)

†Other countries: Australia, New Zealand, Turkey and Russia. ‡ Other countries: Czechia, Hungary, Poland, Slovakia, Japan, Korea, Taiwan, Turkey and Russia.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; N/n, number of patients; Pd, pomalidomide, low-dose dexamethasone; SD, standard deviation.

C2. In Table 19 (page 63), please clarify whether the N figures for Yes and No in each arm are the right way around. The text on page 60 suggests that the N of 16 (Pd) and 2 (IsaPd) should be under 'Yes' instead of 'No' (and therefore, by implication, the N of 42 [Pd] and 50 [IsaPd] should be under 'No' instead of 'Yes').

The company agrees that there was an error in Table 19 as described above. The correct values are provided in a revised table below (Table 27).

Table 28: ICARIA-MM secondary efficacy outcome – OS†– subgroup analyses by further therapy with daratumumab, 4L population

	Pd			IsaPd			HR (95% CI) vs Pd	p-value for interaction‡
	N	Events, n (%)	Median (Months) (95% CI)	N	Events, n (%)	Median (Months) (95% CI)		
All patient	58	23 (39.7)	14.357 (11.565; NC)	52	11 (21.2)	NC (NC; NC)	0.506 (0.245; 1.045)	
Further therapy with daratumumab								0.3496
Yes	16	6 (37.5)	14.357 (7.392; NC)	2	1 (50.0)	NC (4.862; NC)	1.040 (0.117; 9.212)	
No	42	17 (40.5)	NC (8.641; NC)	50	10 (20.0)	NC (NC; NC)	0.441 (0.202; 0.964)	

†Cut-off date: 11th October 2018. ‡Interaction test from the Cox proportional hazard model including the factor, treatment effect and the treatment by factor interaction.
Abbreviations: CI, confidence interval; HR, hazard ratio; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; IPCW, inverse probability of censoring weighting; ITT, intention-to-treat; MM, multiple myeloma; OS, overall survival; Pd, pomalidomide, low-dose dexamethasone.

C3. In Appendix K (page 265), please clarify whether there is a typographic error in the text after Figure 10, where it says that "*Hazard rates during the trial follow-up for PFS for the top six best fitting parametric survival distributions are compared with non-parametric hazards in Figure 11*". The section suggests that it should be TTD instead of PFS.

Yes, this section refers to TTD and not PFS.

Papers excluded that we would like to be sent:

Ahmedzai SH, Snowden JA, Cox A, Cairns DA, Williams CD, Hockaday A, et al. Patient-reported outcomes (PRO) in the setting of relapsed myeloma: The influence of treatment strategies and genetic variants predict quality of life and pain experience. Blood. 2015;126 (23):3180.

Botta C, Ciliberto D, Rossi M, Staropoli N, Cuce M, Galeano T, et al. Network meta-analysis of randomized trials in multiple myeloma: efficacy and safety in relapsed/refractory patients. Blood Adv. 2017;1(7):455-66.

Center for Drug Evaluation Research. Application number 205353Orig1s000: Medical review(s). Food and Drug Administration; 2015.

Center for Drug Evaluation Research. Application number 761035Orig1s000: Other review(s). Food and Drug Administration; 2016.

Corso A. An update of the APEX study. Haematologica Reports. 2006;2(5):2-4.

Dimopoulos MA, Kaufman JL, White D, Cook G, Rizzo M, Xu Y, et al. A Comparison of the Efficacy of Immunomodulatory-containing Regimens in Relapsed/Refractory Multiple Myeloma: A Network Meta-analysis. Clin Lymphoma Myeloma Leuk. 2018;18(3):163-73.e6.

Li J-L, Fan G-Y, Liu Y-J, Zeng Z-H, Huang J-J, Yang Z-M, et al. Long-Term Efficacy of Maintenance Therapy for Multiple Myeloma: A Quantitative Synthesis of 22 Randomized Controlled Trials. Front Pharmacol. 2018;9:430.

Lopuch S, Kawalec P, Wisniewska N. Effectiveness of targeted therapy as monotherapy or combined therapy in patients with relapsed or refractory multiple myeloma: a systematic review and meta-analysis. Hematol. 2015;20(1):1-10.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [ID1477]

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

- 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 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Myeloma UK
3. Job title or position	[redacted]
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 almost entirely on the fundraising efforts of our supporters. We also receive some unrestricted educational grants and restricted project funding from a range of pharmaceutical companies. We are not a membership organisation.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Yes. (Funding amounts to be completed.)

4c. 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: • Structured telephone interviews with relapsed myeloma patients about living with myeloma, their experience and expectations of treatment, and their thoughts on the myeloma treatment pathway. These interviews were focused round the Phase III trial data comparing isatuximab, pomalidomide and dexamethasone to pomalidomide and dexamethasone alone. • 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, 70% of whom had received at least two prior lines of treatment. The study, funded by Myeloma UK and run by the European Medicines Agency (EMA) and University of Groningen, 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.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for	**What is it like to live with myeloma?** Myeloma is a highly individual and complex blood 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. The complications of myeloma can be significant, debilitating and painful and include: severe bone pain,

someone with the condition?	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. - *"I used to travel a great deal for work, including internationally, but that had to stop. A change to working online was forced on us by my diagnosis and working from home does mean that we are now more insular." Patient on 3rd line of treatment* *"The most difficult thing is not being to plan things. I can't predict when I will have a bad night or feel fatigued. That is really hard." Patient with high risk myeloma on 5th line treatment* Multiply relapsed patients, the patient population covered in this appraisal, often experience an even more significant disease burden. They not only face a worse prognosis but also a greater symptomatic burden, due to the progressive nature of the disease and the cumulative effects of treatment which can result in reduced quality of life.[1] *"My wife and I used to cycle tour on our tandem to different parts of the world but since my diagnosis I've had to stop cycling. We haven't been able to have much in the way of holidays. We are tied to that psychological uncertainty of monthly test results. It is difficult getting used to the "new normal" – the fact is it's nothing like the old normal." Patient on 3rd line of treatment* *"The problem with myeloma is that you can set a goal, work towards it but then suddenly when you*

[1] Ramsenthaler, C., Osbourne, T.R. et al (2016) The impact of disease related symptoms and palliative care concerns on health related quality of life in multiple myeloma: a multi-centre study. BMC cancer 16 (1), p. 427

	relapse it's dragged away again." Patient on 3rd line of treatment Studies have also shown that multiple relapses are associated with loss of hope and increasing distress as patients feel that they are exhausting treatment options and "getting closer to the end." [2] For myeloma patients and their families and carers, and particularly those that are multiply relapsed, the worry of whether or not there are further effective treatment options available is a major issue. Knowing that a good treatment will be there when they relapse is hugely important; not having that certainty is a significant psychological burden. - *"The main thing I worry about is, what is next for me? The fact that I might not be able to get access to the latest drugs is the most worrying thing." Patient on 5th line treatment* *"Psychologically, knowing there is another line of treatment out there is very important. To be in a position where you are starting to relapse and there is nothing else out there would be devastating psychologically." Patient on 3rd line of treatment* *"That uncertainty and thinking you might have come to the end of the road that is so worrying." Patient on 5th line treatment* Treatment related adverse events also generally increase with number of lines of therapy; the proportion of patients with one or more toxicity or comorbidity at the end of treatment increases with lines of treatment. - *"In terms of side effects I do still suffer from cramps. My hands cramp up and anything that involves gripping with my hands, like DIY, I can't do. I haven't had a bath for years because I can't feel the temperature of the water. I also have a lot of vertebrae damage and that has really limited what I can do. I was in the meat industry as a senior manager but I just didn't have the energy and had to stop. I was also a competitive runner but had to give that up. Unfortunately I also just "blow up" on steroids. It's very uncomfortable for me going out now because people just don't recognise me. There's no doubt that your life becomes a lot more limited. We've had to completely reconstruct our family life. Infections are also a worry. I'm very uncomfortable in big crowds. Fatigue is a big problem. It's really a struggle to keep interested in doing things. It's tempting to want to just sit and stare at a wall." Patient on 3rd line of treatment." Patient on third line of treatment*

[2] Hulin C., et al (2017) Living with the burden of relapse in multiple myeloma from the patient and physician perspective. Leukaemia research, 59, pp.75-84

That said, patients often see symptoms and side effects as something to be expected and accept it as part of their disease and/or treatment, with many patients developing self-care strategies.[3] - *"I have had a lot of treatment but I'm still up and about, walking and doing what I want to do. Overall I would rate my quality of life highly." Patient at 5th line of treatment*

In summary, many myeloma patients can have durable responses to treatment and good quality of life – but only if they have access to effective and innovative treatments.

*Having access to treatment means I can still be **me**." Patient on 5th line treatment"*

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 Myeloma UK study into the experiences of carers and family members found that looking after someone with myeloma has a significant emotional, social and practical impact:

- 94% of carers are emotionally impacted and found the uncertainty of myeloma a major factor
- 25 per cent of those in work had been unable to work or had to retire early to care for the person with myeloma
- 84 per cent always put the needs of their relative or friend with myeloma before their own;
- Only 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. (The study, "A Life in Limbo" 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.)

[3] Cormican, O. and Dowling, M (2018). Living with relapsed myeloma: Symptoms and self-care strategies. Journal of clinical nursing, 27(7-8), pp, 1713-1721.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers appreciate the wider range of effective treatments that are now available for treating relapsed and refractory myeloma which has delivered significant improvements in survival in myeloma over the past decade. However, myeloma remains a challenging cancer to treat, often particularly so for multiply relapsed patients. Myeloma is a relapsing and remitting cancer which evolves over time and becomes resistant to treatment; a range of treatment options with different mechanisms of action at each stage of the pathway is therefore vital for myeloma patients. The different types of treatment benefit that are most valued by patients are set out below. Each of these benefits will be delivered to a greater or lesser extent by individual treatments currently available on the NHS. The treatments most valued by patients will be those that score most highly on these attributes – particularly the delivery of longer, deeper remissions and, where known, improved survival. • Survival - The lived experience of myeloma patients is of seeking to stay in remission as long as possible; maximising remission at each treatment opportunity is of the utmost importance. A study conducted jointly by Myeloma UK, the EMA and the University of Groningen showed that, achieving a lasting remission from treatment was the most important factor for most (three quarters of all) participants. This was true across all patient groups - this view did not differ across different demographic and clinical characteristics. The data indicated that patients would accept severe side effects if the treatment had a superior efficacy suggesting that efficacy is the strongest driver of treatment choice.[4] – *"Getting those para proteins down and getting a good remission is the most important thing, because ultimately it means living a longer life. " Patient on 5th line treatment* • Response – High response rates are important to patients because it increases the chance of a treatment working when they need it. As it stands if patients fail to respond to a treatment they miss a vital opportunity to prolong their life. A higher probability of a response delivers valued higher levels of confidence about the possibility of achieving meaningful remissions.

[4] Galinsky, J., Fifer, S. and Richard, S., (2017) MYELOMA PATIENT VALUE MAPPING; A DISCRETE CHOICE EXPERIMENT. Haematologica 102, pp600

- Side effects - Patients value treatments with fewer side-effects, of low severity and which do not persist when treatment ends. However, in practice patients will accept varying levels of toxicity in a treatment if it delivers good survival benefit and depending on the stage of their myeloma **-** *"My current treatment regime is tablet based and that is ideal. However if you have to have infusions, you get to the point where you just accept it." Patient on 3rd line of treatment*

- Innovation – Since myeloma becomes resistant to treatment, access to new and different mechanisms of action are very important to patients. Access to innovative treatment also delivers psychological benefits for patients who are encouraged and reassured that they are accessing optimum treatment.
- Treatment administration - Some patients place a high value on oral regimens which give them more control over their day to day lives. However, views on the importance of how a treatment is administered will vary depending on patients' individual circumstances (eg if travel to hospital is difficult due to distance or frailty, or if patients work or look after dependents.) The issue of treatment administration is also inextricably linked to survival benefit. Patients view the inconvenience of hospital visits as a small price to pay when treatments deliver good remission

Finally, due to its relapsing and remitting nature, patients see gains in survival as a "bridge" to further treatments coming down the line – "*The longer you stay well the better chance that another good treatment will come along." Patient on 4th line of treatment*

"Only one benefit for this new treatment for me and that is staying alive for six months… if I could get maybe another drug trial, this and the panobinostat and pomalidomide then that is an extra two years instead of one year. Then maybe by that time something such as the CAR-T cells treatment will have progressed. However long I can extend my life then that is a positive, it is all about staying alive." Patient with high risk myeloma on 5th line treatment

So, the longer remissions are probably what is most important to me. A longer remission means it is more likely new drugs become available. This gives us who are multiply relapsed more options." Patient on 4th line of treatment

8. Is there an unmet need for patients with this condition?	Yes. Multiply relapsed patients face particular treatment challenges and currently there are too few options, especially for patients at fourth line and beyond.[5] Proteasome inhibitors (PI) and immunomodulatory (IMiD) drugs are the most commonly used in treating relapsed myeloma patients. Therefore treatment options for patients previously treated with or refractory to proteasome inhibitors and immunomodulatory drugs are limited. Data has shown that the life expectancy for multiply relapsed myeloma patients with prior treatment with a PI and an IMiD is typically less than 12 months. For patients who are refractory to both a PI and an IMid, median life expectancy is 8-9 months, and for patients who are refractory to three or four of the common PIs and IMiDs median life expectancy decreases to only 3-5 months. [6] The ability to access a triplet combination including a monoclonal anti-body would be of major benefit to patients at this stage in their myeloma. It is very important that an approval for this treatment cover the patient population at fourth line *and beyond* where treatment options become very much more limited. *"What is concerning is I am running out of drugs and treatments. When I was first diagnosed I was given three years and that was fifteen years ago. I have had fantastic treatment but as I go through the lines we are running out of options. It's not clear when and why we can receive certain treatments at certain lines. This is a big bug bear of mine, people who have gone through many relapses are being forgotten about." Patient on fourth line of treatment*

[5] Most patients can be successfully treated at relapse, however, each remission is usually associated with diminishing duration and depth of response over time. If possible combinations of drugs are used compared with initial therapy (Bird, S.A. and Boyd, K., (2019). Multiple myeloma: an overview of management. Palliative Care and Social Practice, 13, p.1178224219868235.)

[6] Gooding S, Lau IJ, Sjeikh M et al, Double Relapsed and/or Refractory Multiple Myeloma: Clinical Outcomes and Real World Healthcare Costs. PLoS ONE. 2015. 10 (9): *e0136207*)

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The key advantages, for the reasons set out above, are PFS gains delivered by the treatment, along with higher response rates. Looking at the attributes most valued by patients and their families and carers: • Survival - Phase III trial data shows that isatuximab, pomalidomide and dexamethasone delivers an additional 5 months of PFS compared to pomalidomide and dexamethasone alone "*The best thing about this treatment combination (isaxtumab, pomalidomide and dexamethasone) is that it keeps your myeloma under control for longer. The side effects don't worry me. They seem less than many and you learn how to cope with them." Patient on 3rd line of treatment* • Response - Response rates were considerably higher than pomalidomide and dexamethasone alone, with the isatuximb triplet delivering an overall response rate of 60.4% *"The fact that this treatment offers a better response rate is very important." Patient on 5th line of treatment* • Innovation - while isaxtumab could not perhaps be described in and of itself as a step change in the treatment of myeloma, the availability of a triplet combination including a monoclonal antibody is a "first" for patients at this stage of their myeloma, where there is significant unmet need • Side effects – There is strong evidence to show that patients will tolerate fairly severe side effects as long as the treatment is delivering in terms of efficacy, although there is of course some variation on an individual basis in terms of what this means in practice. Despite the increasing symptom burden, only 3% of patients at 4th or 5th line choose to discontinue treatment. [7] - *"I have never yet had a time where I have thought seriously about stopping a treatment because of side effects and I find it hard to imagine that I would." – Patient on 5th line treatment*

[7] Yong, K. et al 2016, Multiple myeloma: patient outcomes in real-world practice. British Journal of Haematology, 175(2), pp. 252-264.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Giving the treatment by IV infusion does mean taking time out of the day to attend hospital. For some patients there are cost/capability issues associated with this and it can place an additional burden on carers who have to accompany the patient to hospital. Oral treatments are often valued by patients, particularly those who are working and have dependents. That said, our patient engagement has shown that there are also patients who welcome their treatment being delivery in the safety of a hospital environment and the opportunity to interact with clinical staff and other patients. Overwhelmingly, clinical efficacy and the opportunity of a good remission outweighs any disadvantages in the method of administration. - *"Going to the hospital for an infusion is not a problem for me. I'm used to it and my husband is able to drive me." Patient on 5th line of treatment* *"I have a business to run and that's very disruptive. That said, when you need to be treated and the only treatment available is delivered in the hospital you just get on with it; getting your treatment becomes your job, your purpose." Patient on 3rd line of treatment*
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.	As above it is very important that patients at fourth line and beyond should have the opportunity receive this treatment since treatment options for these patients are currently limited.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission *"It is so disheartening to see reports about new drugs and then realise that you can't have it. I don't believe that the needs of multiply relapsed patients are met at the moment. We don't have enough treatment options. Why can't I get access to the latest drugs? You shouldn't have poorer options just because you have relapsed more times. I am only 60, my bloods are good, I have a good quality of life. I don't agree that I shouldn't be able to have a treatment that someone less fit can have just because they have had fewer treatments than me. I don't want to be treated as a number. I want to be treated as a person with access to treatments that meet my needs." Patient on 5th line treatment*	

- Isatuximab, pomalidomide and dexamethasone delivers a PFS gain which is highly valued by patients and their families and carers and it should be made available as a treatment option. The higher response rate is also important to patients and delivers benefits in terms of certainty
- There is a clear and significant unmet need for multiply relapsed patients who face a higher disease, toxicity and psychological burden. It is important that this treatment be made available for patients, including those beyond fourth line. A triplet combination including a monoclonal anti- body is a significant positive addition to the treatment options available to multiply relapsed patients
- Patients value the efficacy of the treatment above any possible inconvenience in the method of administration and consider the side effect profile to be tolerable.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [ID1477]

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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- 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	[redacted]
2. Name of organisation	**Guys and St. Thomas' NHS Foundation Trust / UK Myeloma Forum**

3. Job title or position	**Consultant Haematologist / Advocacy Lead**
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).	**Medical / Nursing professional organisation for healthcare professionals who diagnose, treat and support patients with myeloma. Charitable funds underpinned by bequeathed monies, monies raised via attendance at educational meetings and unrestricted pharma grant monies**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and	**yes**

purpose of funding.	
5c. 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 stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Myeloma is an incurable cancer of the bone marrow. It follows a responding and relapsing course with patients eventually developing resistant / refractory disease that is unresponsive to therapy. Most patients diagnosed with myeloma will die as a result of their myeloma. The main aims of treatment are: 1. to alleviate symptoms / clinical problems of the disease (bone pain & fractures, bone marrow failure e.g anaemia, renal failure, recurrent infections) and thereby improve quality of life; 2. Control the disease by effecting an objective response 3. Stopping /delaying progression and 4. Extending life
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.)	Response is measured in a number of ways – as defined by the International Myeloma Working Group. The main overall response is measured by changes in the serum paraprotein or serum free light chains levels. A clinically significant response is achievent of a partial response (PR) by IMWG criteria or better – this represents a 50% reduction in disease burden. The depth of response is associated with quality of clinical response, length of response and overall survival so that Minimal residual disease negative response (MRD negative - equivalent to no detectable disease using the most sensitive flow cytometric or genomic methods) is better than complete response (disappearance of serological markers) which is better than >90% reduction in serological markers (termed Very good partial response – VGPR) and that in turn is better than 50 – 90% reduction in serological markers (termed Partial response – PR). Clinical responses can also occur with an improvement in anaemia, or renal failure

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – this is an incurable disease with eventual development of drug resistance. There is a need to treatments that can give long term disease free survival or disease control with manageable side effect profile
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?	Yes – British Society of Haematology & NICE guidelines / technology appraisals dictate what therapies can be used at which time points.
• 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.)	There are variations on the basis of the initial (at diagnosis) medical suitability of the patient to undergo stem cell transplant (i.e. patients are initially treated as either transplant eligible or transplant ineligible) according to specific NICE appraisals. Subsequent therapies at relapse are determined by both the specific drugs that patients have received already and their response to those drugs. There are currently up to 6 lines of therapy available according to the various NICE guidelines (1st line: TA311, TA228, TA587, 2nd line: TA457, TA573, TA586, TA129, 3rd or 4th line: TA171, TA505, TA380, 4th line only: TA510, 4th line+: TA427. There are some variations between professionals on where individual components should be placed but there is limited scope for variation within the NICE "algorithm" until 3rd line therapy.
• What impact would the technology have on the	This therapy combines a new anti-CD38 monoclonal antibody (isatuximab) with an existing therapy, pomalidomide / dexamethasone – the subject of TA427. I would expect the introduction of this combination

current pathway of care?	to replace daratumumab monotherapy and pomalidomide / dexamethasone therapy (TA510, TA427) where it is appropriate to use it. I would expect it to be considered within the current UK context as a 3rd line or 4th line drug (after prior treatment with proteasome inhibitor – bortezomib and immunomodulatory drug – lenalidomide). Rarely it may be considered earlier (2nd line) in patients who have had exposure to certain drugs as part of clinical trials at 1st line.
10. 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?	It would effectively combine 2 therapy approaches currently used at 4th line and 5th line (daratumumab and pomalidomide / dexamethasone). With recent changes in NICE guidance that allows earlier (1st line or 2nd line) use of lenalidomide there is a need to consider pomalidomide based treatment from 3rd line onwards. The infusion component of treatment is shorter and thereby more cost effective than existing therapy (daratumumab) and the published side effect profile is not significant increased by the combination of isatuximab with poma / dexa
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics (haemato-oncology or myeloma clinics)
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None – this technology is an adaptation of existing treatment approaches

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – Phase 3 trial (ICARIA) demonstrates it is significantly better than either pomalidomide / dex alone (the subject of the phase 3 trial) or anti-CD38 monoclonal antibody monotherapy (as published in phase 2 trials in terms of response rates (approx. double the overall response rate) and progression free survival (approx. double the PFS). It is also clearly recognised in myeloma that a significant proportion of patients are not able to be offered therapy (due to poor performance status, symptom burden) with each subsequent line such that <10% of diagnosed patients will eventually be able to receive a 5th line therapy. Combining 2 effective approaches ensure more patients are able to access effective therapy at an earlier time point.
• Do you expect the technology to increase length of life more than current care?	Yes- initial albeit early follow-up data suggest a strong statistically non-signficant trend towards overall survival improvement (10% improvement in survival at 12 months follow-up). Extended follow-up is likely to confirm that this is the case.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – relieving the symptom burden in myeloma has significant benefit in terms of quality of life. However, demonstrating this is a statistically meaningful way in myeloma has always been very difficult.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No benefits appear to be present across the whole spectrum of patients with multiple relapsed myeloma.
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 affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No – compared with existing daratumumab this is likely to be easier – less infusion related reactions, shorted infusions, less intensive administration schedule.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	If objective evidence of progression using serological markers (paraprotein) then treatment would be stopped
15. Do you consider that the use of the technology will result in any substantial health-	Not specifically

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
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?	Yes – this combines 2 different classes of treatment successfully for a late stage group of patients
• 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?	It improves overall responses (60%) at a time when they are low (<35%) and at a time when patients are beginning to develop significant myeloma related co-morbidities

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?	Not significantly different from current treatment
Sources of evidence	
18. 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?	ORR, PFS, OS, MRD negative rate
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	PFS and MRD is a good surrogate marker for long term outcome

• 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 recent NICE technology appraisal guidance?	No
21. How do data on real-world experience compare with the trial data?	Not available
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

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Excellent combination therapy
- Improves disease control at earlier time point
- More patients able to gain benefit
- Excellent use of health resources
-

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NHS England submission on the NICE appraisal of isatuximab in combination with pomalidomide and dexamethasone in patients with myeloma previously treated with 3 lines of chemotherapy (ID1477)

The comparator for isatuximab-pomalidomide-dexamethasone

1. NHS England notes that the marketing authorisation for isatuximab will be in patients with relapsed/refractory myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (bortezomib or carfilzomib or ixazomib) **and** have demonstrated disease progression on the last therapy.
2. The treatment pathway in English clinical practice has changed considerably in the last months as lenalidomide plus dexamethasone is now available as a once-only treatment in 3 places in the treatment pathway: to the treatment-naïve or the 1 prior or the 2 prior populations. In the absence of consideration of the three much used CDF-recommended drugs/combinations (daratumumab+bortezomib+dexamethasone in the 1-prior, ixazomib+lenalidomide+dex in the 2 and 3 prior and daratumumab monotherapy in the 3 prior populations), there is now a potential 'gap' in the treatment pathway for patients who have received lenalidomide- and proteasome inhibitor-based treatments in their first 2 lines of therapy. The clinical view would opt for pomalidomide plus dexamethasone in the 2-prior population but pomalidomide plus dexamethasone is only recommended by NICE in the 3 or 3+prior population. Panobinostat plus bortezomib plus dexamethasone is recommended by NICE in the 2 or 2+ prior population and thus could in theory fill the 2-prior space in the treatment pathway. However, clinical choice has relegated it to follow pomalidomide as panobinostat has troublesome gastrointestinal toxicity and also because clinicians have regarded the main use of panobinostat plus bortezomib plus dexamethasone as being a way of accessing re-use of bortezomib. This latter advantage has fallen away as NHS England has allowed re-use of bortezomib for a number of years.
3. The consequences of the above discussion are twofold. One upshot is that NHS England should address the question of the treatment options in the 2-prior population. NHS England notes with disappointment that Sanofi has chosen to restrict its submission for the NICE appraisal to the 3-prior population despite the majority of patients in the ICARIA trial being 2-prior. The second outcome is that the comparator for isatuximab plus pomalidomide plus dexamethasone in the 3-prior population is currently pomalidomide plus dexamethasone as this is the regimen that is used in at least 90% of the 3-prior population in England, whereas 10% or less of patients receive panobinostat plus bortezomib plus dexamethasone in the 3-prior setting.

Previous treatment with anti-CD 38 antibodies

4. Isatuximab and daratumumab are anti-CD38 antibodies. The ICARIA trial excluded patients who had been treated with a previous anti-CD38 antibody and who had progressed during or within 60 days of anti-CD38 treatment. There are very strong

grounds on the basis of biological plausibility for a high degree of cross resistance between daratumumab and isatuximab and as a consequence when the EAMS scheme for isatuximab plus pomalidomide plus dexamethasone was set up, treatment was restricted to patients who were either anti-CD38 antibody-naïve or had not progressed during or within 60 days of treatment with an anti-CD38 antibody. Since daratumumab is a well tolerated drug from the toxicity point of view and thus few patients would discontinue the drug without having progressed on it, it is no surprise to NHS England that 96% of the patients in the isatuximab EAMS scheme were treatment naïve to an anti-CD38 antibody. NHS England does not regard the current isatuximab randomised trial evidence base to be relevant to patients who have progressed on an anti-CD38 antibody and thus would wish any NICE recommendation to exclude this group of patients.

Immaturity of overall survival and progression free survival data

5. NHS England notes that the median duration of follow up in the ICARIA trial is currently only 11.6 months. For this submission by the company, the overall survival data is 32% mature and the progression free survival data has only had about 50% of events. Data analysis for efficacy had a cut off on 11 October 2018, this being a long time ago. In addition, NHS England notes that the ITT PFS KM curve for isatuximab flattens just above the median value with a considerable number of censored patients on this plateau.
6. So far, the OS data shows a non-significant statistical difference between arms in the ICARIA trial in the ITT population (HR 0.69, 95% CI 0.46-1.02). Whilst NHS England notes that further survival data will be reported in 2021 and expects this ITT OS data to be statistically different (at least if subsequent daratumumab is allowed for), NHS England is less certain as to whether the timing of this analysis will address the committee's uncertainties as to how the OS data should be modelled in the longer term.

Post hoc analysis for progression free survival

7. NHS England observes that the post hoc analysis for PFS in the 3-prior subgroup (which was not a stratification factor) does not show any statistical difference between the 2 arms in the ICARIA trial (HR 0.60, 95% CI 0.35-1.03). The same applies to OS: HR 0.49 (95% CI 0.24-1.02).

Cost effectiveness

8. NHS England notes that the company chose the exponential model to extrapolate for overall survival despite the fact that 2 of the 3 clinical experts it consulted chose the Weibull function. NHS England also observes that the company used the restricted log normal function to extrapolate PFS even though none of the 3 clinical experts chose this particular extrapolation.

9. GCSF prophylaxis was modelled to occur in 43% of patients in both arms in the cost effectiveness analysis. NHS England considers such a high level of GCSF use to be unlikely in England.
10. The subsequent treatments used in the model may reflect the trial data but do not reflect practice in England. Daratumumab monotherapy is only available from the CDF as 4th line treatment (ie use is in the 3 prior patients); carfilzomib can only be used 2nd line, lenalidomide can only be used in the 1st, 2nd and 3rd line places in the myeloma treatment pathway and prescribing of bendamustine is uncommon.

Cancer Drugs Fund

11. The uncertainties in outcomes in this appraisal are substantial as to the impact on PFS, the survival gain, the modelling of both PFS and OS and the use of subsequent therapies as 5th line treatments and beyond. Any real world data from the CDF is going to be modest, partly because of the likely time duration of any sojourn in the CDF for isatuximab-pomalidomide-dexamethasone and partly because the eligible population is shrinking as a consequence of prior daratumumab given as 2nd line therapy. The vast majority of patients stopping CDF 2nd line daratumumab will do so with disease progression. The biological plausibility argument in the absence of robust clinical data is very strong in patients previously treated with daratumumab for expecting little additional benefit from subsequent isatuximab over and above what pomalidomide would have provided. NHS England does not regard the CDF as a mechanism for providing the company with clinical data on outcomes with isatuximab in patients progressing on daratumumab. If this is a relevant clinical question, then the company should be designing proper clinical trials to address the data gap.

Prof Peter Clark

National Clinical lead for the Cancer Drugs Fund

NHS England

May 2020

NICE National Institute for Health and Care Excellence

Patient expert statement

Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [ID1477]

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 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 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 10 pages.

About you	
1.Your name	ALAN CHANT
2. Are you (please tick all that	☐ ✓ a patient with the condition? ☐ a carer of a patient with the condition?

apply):	☐ ✓ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Myeloma UK
4. Did your nominating organisation submit a submission?	☐ ✓ yes, they did ☐ no, they didn't ☐ I don't know
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.)	☐
7. How did you gather the information included in your statement? (please tick all that apply)	☐ ✓ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ ✓ I have other relevant personal experience. Please specify what other experience: I am a Trustee of Myeloma UK ☐ ✓ I am drawing on others' experiences. Please specify how this information was gathered: Knowledge of the Myeloma UK, EMA and University of Groningen quantified trade-off study of 560 myeloma patients on preferences for PFS versus two levels (mild and severe) of toxicity reductions (published in The Oncologist 2018). As a member of a Myeloma Support Group (Reading) and having discussions with myeloma patients at meetings and conferences. Wider knowledge of cancer patients resulting from being a previous Trustee of Cancer Research UK (CRUK) and the National Cancer Research Institute (NCRI), and as a patient representative on a number of clinical research organisations.
Living with the condition	
8. What is it like to live with the	I was diagnosed with myeloma in 2011 and am currently in remission (since mid-2016) following third line

condition? What do carers experience when caring for someone with the condition?	treatment. My treatment regime to date has included radiotherapy, CDT, stem cell transplant, proteasome inhibitors (Carfilzomib and Ixazomib), IMiDS (Revlimid), biopsies and numerous scans. My initial symptoms were back pain and a collapsed spine, which required an emergency operation to stabilise the spine with titanium rods. I was a hospital inpatient for 17 weeks. Neural damage resulted in me being initially bed-ridden and then receiving rehabilitation and physiotherapy in order to learn to walk again. I have still lost some 30% of feeling in my legs as a result of neurological damage, and walking for long distances is a problem. Throughout my treatment regime I have endured spinal pain, thigh pain and infections (such as UTIs and sepsis) from the disease, and insomnia, fatigue, nausea and other toxicities from the drugs. Like many myeloma patients, the impact on my business life was to curtail thoughts of full-time employment. I had been a main board Director in five companies including responsible for marketing, communications, IT, business development and change management. I had been in a position of creating and managing successful change in commercial companies and providing certainty of outcomes; the uncertainty and lack of control that myeloma injected into my life was therefore a significant shock. Domestically I have learnt to rely more heavily on my wife (for shopping, paying service suppliers, jobs around the house, gardening etc) and to employ contractors for work I would have undertaken myself. It has changed our relationship from that of husband / wife to myeloma patient / carer. Carers have an important supporting role to play and they suffer the burden of accompanying patients to hospital visits and picking up the jobs that the patient can no longer undertake. Socially I have had to reduce my ability to commit to social engagements in the near-to-middle future in case I become unwell (e.g. holidays, Christmas occasions booked in advance). As a result of kidney and bladder problems associated with the cancer, I have to use drainage bags during the day and the night. My wife and I have not taken a holiday for the last nine years – not wanting to be risk being taken ill abroad or expose me to potential problems in unfamiliar circumstances (e.g. walking issues, risk of falling

	etc). Physically, I have had to learn to deal with fatigue and the other side effects of the disease and the toxicities of drugs. Psychologically, I have had to learnt to deal with the relapse/remission cycle and the level of perceived well-being being determined by the results of the latest blood test, biopsy or scan. The focal point of my diary is hospital visits, which involves a 70-mile round trip every 4 weeks, taking up most of the day, and in the past I had more frequent visits when I was on a clinical trial (Carfilzomib). Some patients find the time and financial aspects of the cost of travelling an issue, especially when drugs need to be administered intravenously. As a result of the good treatment that I have received from the NHS, and to pay something back, I have become a patient representative on numerous research organisations, including Myeloma UK, CRUK, NCRI and Oxford BRC. This has enabled me to take back some of the control that myeloma has taken from me and enabled me to learn more about my condition. Currently, in remission after third line treatment, I am aware that 4th line treatment is very personal to me. At this stage, myself and other myeloma patients are aware that we are nearing the end game of our battle against the disease. Life becomes very important at this stage and psychology plays an important part, involving hope and determination balanced by fear, uncertainty and lack of control. The knowledge and reassurance that there is a drug treatment that is regarded as the very best available to continue to provide effective treatment and quality of life for a few more years with our loved ones is very important.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and	Treatment and care from consultants and nurses for myeloma patients is extremely good. Personally, I have received exceptional treatment at the Churchill Hospital in Oxford. The availability of numerous drugs from which consultants can choose from is desirable, given that some

care available on the NHS?	patients respond better than others to some drugs (both with regards efficacy and tolerance). This is important both on medical grounds, but also reassuring on psychological grounds that provide the patient with continuing hope of managing the disease for as long as possible. Drugs that have less side effects are vital for the quality of life of the patient. Survival benefits of a drug are long term and unknown to the patient, but adverse side effects are immediate and can substantially impact on daily life. Over the last six years the availability of drugs to treat myeloma has improved, and patients are grateful to have the opportunity of their consultants choosing and prescribing the right drug for them at the right time.
10. Is there an unmet need for patients with this condition?	I believe that prior to the last three years there was a paucity of approved drugs for 4th line myeloma treatment for relapsed and refractory patients. Although this has improved with the approval of Daratumumab, Pomalidomide and Ixazomib combinations there is still an unmet need for even more effective drugs at this line of treatment. I believe that the ICARIA trial has demonstrated that the addition of Isatuximab to the Pomalidomide/Dexamethasone doublet has demonstrated better response in patients and longer PFS. We are also aware from US experience and FDA approval that a monoclonal antibody drug (such as Daratumumab) works better in triplet combinations. The Isa/Pom/Dex combination is therefore better for patients that two of the current approved treatments.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	According to the Phase III ICARIA trial undertaken across 24 countries the Isa/Pom/Dex approved combination, compared to Pom/Dex alone, provided better patient response rates (60.4% vs 35.3%), longer PFS (11.5 months vs 6.5) and an indication of long overall survival of around 10%. Patients are also aware that it has been proved that drug combinations (doublets and triplets) perform better than drug monotherapy along because all drug types have different methods of action on cancer cells – and combinations are more therefore more effective in killing the cancer cells. In this situation of

	addressing 4th line treatment, the following is therefore likely: 1. The Isa/Pom/Dex triplet will be more effective than Dara monotherapy. 2. The unique combination of a mAB + IMiD + Dex is the first such combination of treatment for myeloma patients – and stands a good chance of being successful.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	The ICARIA trial also indicated the higher likelihood of toxicities (86.8% for Grade 3+ vs 70.5%). However, to counter this potential problem for patients the following should be noted: 1. The higher rate of side effects did not result in more patients discontinuing the treatment. It was actually slightly less (7.2% vs 12.8%). 2. A trade-off study conducted by Myeloma UK, EMA and the University of Groningen in 2016 concluded that patients overwhelmingly preferred improvements in PFS over two levels of reductions in toxicities. Patients will therefore tolerate side effects if it results in better efficacy.
Patient population	
13. 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.	Patients about to embark on 4th line treatment will benefit. This is an extremely distressful time for relapsed and refractory myeloma patients. Patients, their carers and family members are aware that they are nearing the end of their cancer journey. It is important to know that there is an effective treatment that will provide a few more months or years of life together.

Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None apparent.
Other issues	
15. Are there any other issues that you would like the committee to consider?	None
Key messages	

16. In up to 5 bullet points, please summarise the key messages of your statement:

- **Efficacy:** This drug combination is more effective than currently approved drugs for 4th line treatment. More effective than Pom/Dex alone (ICARIA trial) for both response rates and PFS. More effective than Daratumumab monotherapy (US experience).
- **Tolerability:** The likely toxicities are tolerable and acceptable, especially given the gain of improved PFS. Infusion times are also shorter than the other anti-CD38 monoclonal antibody (Daratumumab).
- **Unmet need:** Patients at 4th line treatment are coming to the end of their myeloma journey and deserve the best possible treatment regime to give them a few more months / years of life and relieve their psychological burden.
- **Triplet treatment:** A unique combination regime of mAB + IMiD + Dex, each of which has a different method of action on myeloma

cancer cells and a higher chance of success.

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Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [ID1477]

Clinical expert questions

Abbreviations used:

ISA/POM/DEX: Isatuximab with pomalidomide and dexamethasone

POM/DEX: Pomalidomide with dexamethasone

PANO/BORT/DEX: Panobinostat with bortezomib and dexamethasone

1. What do you consider to be standard treatment options at 3rd, 4th and 5th line in NHS clinical practice for relapsed or refractory multiple myeloma? (Please bear in mind that NICE do not consider drugs recommended via the Cancer Drugs Fund (CDF) to be part of current routine NHS clinical practice). Any comments on the relative use of each listed treatment, at each line, would be helpful if possible.

   Answer:

3rd line treatments	4th line treatments	5th line treatments
Stem-cell transplant eligible: • LEN/DEX • IXA/LEN/DEX (CDF only) Stem-cell transplant ineligible: • Bridge treatment • Small proportion PANO/BORT/DEX	POM/DEX DARA (CDF only) [clinical outcomes perhaps not as good as expected]	No standard treatments, likely response to treatment is very low at 5th line. POM/DEX may be given if DARA given 4th line PANO/BORT/DEX may be tried

2. The company have positioned isatuximab with pomalidomide and dexamethasone (ISA/POM/DEX) as a 4th line treatment option for relapsed or

refractory multiple myeloma. They state this is based on a high unmet need at this part of the treatment pathway.

Do you agree that the most appropriate position in the treatment pathway for ISA/POM/DEX is as a 4th line treatment (i.e after 3 relapses)?

Are any other parts of the treatment pathway also appropriate for treatment with ISA/POM/DEX?

Answer:

4th line is the most appropriate position for ISA/POM/DEX, due to the unmet need. Expect that the majority of ISA/POM/DEX use would be at 4th line.

Many current patients receive ixazomib with lenalidomide and dexamethasone or lenalidomide and dexamethasone at 3rd line There is currently no standard treatment at 3rd line for patients who are not eligible for stem-cell transplant and have had both lenalidomide and bortezomib earlier in the pathway. A bridge treatment is needed before moving on to 4th line. A small group of people may receive ISA/POM/DEX if they have received both lenalidomide and bortezomib at previous lines.

Lenalidomide uptake at 1st line is increasing, and is becoming standard of care for newly diagnosed transplant ineligible patients, but has only recently been available at the earlier parts of the pathway. Lenalidomide uptake is around 80% for newly diagnosed transplant ineligible patients.

3. In the pivotal clinical trial (ICARIA-MM), an exclusion criterion was refractory to a prior treatment with an anti-CD38 monoclonal antibody (such as daratumumab). How does this impact the generalisability of the results of the ICARIA-MM trial to NHS clinical practice?

   Would you use ISA/POM/DEX as a treatment option in people with relapsed or refractory multiple myeloma if they had previously received an anti-CD38 monoclonal treatment and were refractory to it?

   Would you use ISA/POM/DEX in people with relapsed or refractory multiple myeloma if they had previously received an anti-CD38 monoclonal treatment but were not refractory to it?

   How would previous treatment with an anti-CD38 monoclonal impact the effectiveness of an anti-CD38 monoclonal antibody given at a later line of treatment?

Answer:

It is appropriate for the eligible population for ISA/POM/DEX to match that of the ICARIA-MM clinical trial. Therefore, ISA/POM/DEX should not be used in people who have received prior treatment with, and were refractory to, an anti-CD38 monoclonal treatment. If they received prior anti-CD38 treatment, and were not refractory to it, then ISA/POM/DEX can be given. There are different reasons why treatment may be stopped without being refractory to it including practical issues around getting into hospital for treatment or side effects.

While there may be some clinical rationale to have a line of treatment with a non-anti-CD38 based treatment in between treatment anti-CD38 based treatments, it would not be fair to exclude patients solely on this point, so a treatment break should not be enforced.

4. Is panobinostat with bortezomib and dexamethasone (PANO/BORT/DEX) a relevant comparator for ISA/POM/DEX at 4th line considering current routine NHS clinical practice? [Please bear in mind that NICE do not consider drugs recommended via the Cancer Drugs Fund (CDF) to be part of current routine NHS clinical practice].

   How often is PANO/BORT/DEX used in clinical practice at 4th line [bearing in mind the above statement on CDF drugs]?

   Please describe the decision-making process when deciding between POM/DEX and PANO/BORT/DEX as treatment options?

   Answer:

   PANO/BORT/DEX is not a standard of care option at 4th line due to its toxicity and lack of efficacy compared to POM/DEX. Often patient may have developed previous peripheral neuropathy due to Bortezomib, preventing the use of PANO/BORT/DEX. Furthermore patient are often refractory of Bortezomib at this stage leading to very poor clinical outcomes with PANO/BORT/DEX. It may be given as a 3rd line treatment to fill a treatment gap before a patient reaches 4th line, but POM/DEX would almost always be given instead of PANO/BORT/DEX at 4th line. At 4th line, patients will already have been treated with bortezomib, with some having been exposed twice before, so even less reason to give PANO/BORT/DEX at 4th line.
   There was a short time where POM/DEX was unavailable so PANO/BORT/DEX or bendamustine was used at 4th line but that was due to

the circumstance but POM/DEX is now available through routine commissioning.

5. Please consider the table below and provide estimates on the expected proportion of people with multiple myeloma at 4th line of treatment (previously failed 3 treatments) alive at each of the below timepoints. Ranges can be reported and please indicate how certain these estimates are.

Proportion of people with MM at 4th line of treatment (%) alive at x years	Isatuximab with pomalidomide and dexamethasone	Pomalidomide and dexamethasone	Panobinostat with bortezomib and dexamethasone
1 year	65%	55%	40%
2 years	40%	33%	20%
5 years	20%	15%	10%
10 years	<5%	<5%	<2%
20 years	0%	0%	0%

Answer:

Estimates listed above are uncertain and this should be noted.

6. What is the average life expectancy for people with relapsed or refractory multiple myeloma who have failed 3 prior lines of therapy? Please also comment on the level of certainty surrounding your answer.

Answer:

Published data shows that median life expectancy with POM/DEX at 4th line is around 13.7 months (Maciocia et al 2017), which matches clinical trial data. Another study (Kumar et al) states that median survival in patients who are refractory to both an IMiD (lenalidomide or pomalidomide) and a PI (bortezomib or carfilzomib), and an alkylating agent is 13 months (CI interval 11 to 15 months).

7. In your opinion, what level of drug wastage would be associated with both ISA/POM/DEX and POM/DEX? Is an assumption of no drug wastage an extreme/unlikely scenario?

   Answer:

   Unsure. The level of vial sharing depends on different aspects, such as stability of the substance, size of the clinic and frequency of treatment. Commissioners may move towards dose banding but perhaps this is not an issue for NICE.

8. Please comment on the likely difference in adverse events between ISA/POM/DEX and POM/DEX. Is there a possibility of more rare and serious adverse events when treating with ISA/POM/DEX compared with POM/DEX.

   Answer:

   Rare and serious adverse events are not expected to be significantly higher in the ISA/POM/DEX arm compared to the POM/DEX arm, based on clinical experience with anti-CD38 anti monoclonal antibodies. Haematologists are familiar with combination therapies and most adverse events are managed very well.

9. Pomalidomide exposure was higher in the POM/DEX arm compared to the ISA/POM/DEX arm. This may have been due to the open-label nature of the trial. Can you comment on the likely impact of the difference relative dose intensities between the ISA/POM/DEX and POM/DEX arms on the generalisability of the trial results to clinical practice in the NHS?

   Answer:

   No comment and not explored further by NICE technical team.

Any additional comments:

There is a high unmet need in this population and ISA/POM/DEX would be a welcomed as a well-tolerated therapy option by clinicians and patients.

Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma. A Single Technology Appraisal.

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Date completed	21/01/2020

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 12/97/72.

Declared competing interests of the authors

None of the authors has any conflicts of interest to declare. Conflicts related to our clinical advisors are presented in the acknowledgements.

Acknowledgements

We would like to thank Paul Tappenden, ScHARR, for providing comments on the draft report and Andrea Shippam, Programme Manager, ScHARR, for providing administrative support and in preparing and formatting the report. We would also wish to thank the following clinicians who provided expert advice to the ERG: Dr Jim Cavet, Consultant Haematologist and Honorary Senior Lecturer, The Christie NHS Foundation Trust; Dr Osbourne, Consultant in Palliative Medicine and Lead for Research Governance, St. Joseph's Hospice; Dr Parrish, Consultant Haematologist, Leeds Teaching Hospitals NHS Trust; and Professor Pratt, Consultant Haematologist and Honorary Professor of Haematology, University Hospitals Birmingham NHS Foundation Trust.

Dr Cavet participated in an advisory board related to isatuximab for Sanofi in May 2014, received financial support to attend a workshop in Boston, USA and to set up a database related to daratumumab treated multiple myeloma outcomes from Celgene, He is an investigator in the MAIA3008/3011 studies and was involved in setting up the CARTITUDE4 trial, both associated with Janssen Cilag. Dr Parrish received financial support from Celgene to attend a meeting. Dr Osbourne received an honorarium from Janssen Cilag to deliver a teaching session at a National Conference. Prof Pratt has received honoraria from Celgene and Janssen Cilag.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Stevenson M, Hock E, Stevens JW, Navega Biz A, Orr M, Wong R. Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma: A Single Technology Appraisal. School of Health and Related Research (ScHARR), 2020.

Contributions of authors

Ruth Wong critiqued the company's search strategy. Emma Hock summarised and critiqued the clinical effectiveness data reported within the company's submission. John Stevens and Martin Orr critiqued the statistical aspects of the submission. Matt Stevenson and Aline Navega Biz critiqued the health economic analysis submitted by the company. All authors were involved in drafting and commenting on the final report.

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Abbreviations

3L	Third-line
4L	Fourth-line
5L	Fifth-line
AE	Adverse event
BIC	Bayesian Information Criterion
BNF	British National Formulary
BOR	Best overall response
BSA	Body surface area
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CDF	Cancer Drugs Fund
CS	Company's submission
CSR	Clinical Study Report
DCO	Data cut-off
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DVd	Daratumumab, bortezomib and low-dose dexamethasone
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire with 30 items
EORTC-QLQ-MY20	European Organisation for Research and Treatment of Cancer Quality of Life Multiple Myeloma Specific Module with 20 items
EOT	End of treatment
EQ-5D-5L	EuroQoL Group self-report questionnaire with 5 dimensions (3 level)
EQ-5D-5L	EuroQoL Group self-report questionnaire with 5 dimensions (5 level)
ERG	Evidence Review Group
GEE	Generalised estimating equation
GHS	Global health status
HR	Hazard ratio
HRQoL	Health-related quality of life
ICARIA-MM	Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma

ICER	Incremental cost-effectiveness ratio
IMWG	International Myeloma Working Group
IRC	Independent Response Committee
IRT	Interactive response technology
IsaPd	Isatuximab, pomalidomide and low-dose dexamethasone
ISS	International Staging System
KM	Kaplan-Meier
LYG	Life year gained
MAIC	Matching-adjusted indirect comparison
MM	Multiple myeloma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
ORR	Overall response rate
OS	Overall survival
PanVd	Panobinostat, bortezomib, dexamethasone
PAS	Patient Access Scheme
Pd	Pomalidomide and low-dose dexamethasone
PFS	Progression-free survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Services
QALY	Quality-adjusted life year
RCS	Restricted cubic spline
RCT	Randomised controlled trial
RDI	Relative dose intensity
RRMM	Relapsed and/or refractory multiple myeloma
SAE	Serious adverse event
SD	Standard deviation
STA	Single Technology Appraisal
TEAE	Treatment-emergent adverse event
TTD	Time to treatment discontinuation
TTP	Time to progression

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company provided an appropriate description of multiple myeloma (MM), with a focus on relapsed and refractory MM (RRMM), the current practice guidelines regarding lines of treatment and the potential positioning of isatuximab, pomalidomide and low-dose dexamethasone (IsaPd) in the treatment pathway. The proposed positioning of IsaPd in the company base case was narrower than the anticipated market authorisation, with the company assuming that IsaPd would be used in patients who have received after three prior lines of treatment, including lenalidomide, and would be used in fourth-line (4L) rather than in third-line. The main comparator was assumed to be pomalidomide and low-dose dexamethasone (Pd) although to fulfil the NICE scope a comparison was made against panobinostat, bortezomib and dexamethasone (PanVd). The company stated that it did not believe that PanVd was an appropriate comparator due to the toxicity associated with this intervention.

Expert clinical opinion provided to the ERG was divided on whether PanVd was an appropriate comparator for IsaPd. One clinician stated that PanVd was rarely used due to toxicity and the perceived lack of response compared with alternative therapies, however, other clinicians stated that PanVd was used in several units and that toxicity concerns would be managed with changes to the dose or schedule. Whilst these experts stated that PanVd was generally used at fifth-line (5L) this was because daratumumab monotherapy is only permitted to be used, via the Cancer Drugs Fund (CDF) as a 4L treatment. However, were daratumumab monotherapy not available, as NICE do not consider drugs within the CDF to be comparators, these clinicians stated that PanVd would be used at 4L.

1.2 Summary of the clinical effectiveness evidence submitted by the company

The clinical evidence relating to IsaPd for treating RRMM is based on the ICARIA-MM trial, a Phase III open-label randomised controlled trial (RCT) of patients with at least two prior lines of treatment. The ERG is confident that no additional studies (published or unpublished) of IsaPd for treating RRMM are likely to have been missed.

The ERG is confident that the relevant population, intervention and comparator have been included in the company's submission (CS). The primary outcome of the ICARIA-MM trial was progression-free survival (PFS), assessed from the date of randomisation to the date of first documentation of progressive disease or the date of death from any cause, whichever came first, at the cut-off date (11th October 2018), which is an acceptable primary outcome according to the European Medicines Agency (EMA), provided that overall survival (OS) demonstrates a trend towards superiority. In the 4L population, the median PFS was greater in the IsaPd arm (13.31 months [95% CI: 7.425, not calculable]) than in the Pd arm (7.82 [95% CI: 4.468, 11.072]), and the stratified (by age) hazard ratio

(HR) was 0.598 (95%: CI 0.348, 1.030, p=0.0611), which the CS states represents a 40.2% risk reduction of disease progression or death in favour of IsaPd compared with Pd. The EMA suggests that OS should demonstrate a trend towards superiority if PFS is used as a primary outcome. Mortality events were reported in 21.2% and 39.7% of 4L patients in the IsaPd and Pd arms, respectively, with a median OS of 14.36 months (95%: CI 11.565, not calculable) in the Pd arm whilst the median OS had not been reached in the IsaPd arm (stratified HR 0.494 [95% CI 0.240, 1.015], p=0.0502), which indicates a trend for greater median OS in the IsaPd arm. However, the OS data were immature and final OS analyses are planned once 220 deaths have been observed (anticipated in Q2 2021). In the 4L population, there were 34 death events; 11 (21.2%) in the IsaPd arm and 23 (39.7%) in the Pd arm at data cut-off. The effect of IsaPd on OS may have been impacted by an imbalance between the trial arms in the proportion of patients who received subsequent daratumumab. Overall response rates and median time to progression were higher in the IsaPd arm of the 4L population than the Pd arm. The median duration of response was not calculable for both the IsaPd and Pd arms in the 4L population, and no clinically meaningful difference between treatment arms on European Organisation for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire with 30 items (EORTC-QLQ-C30) scores and subscale scores, suggesting no quality of life detriment of IsaPd in relation to treatment with Pd. In terms of adverse events, IsaPd appears to be generally well tolerated.

IsaPd and PanVd were not part of a connected network of evidence and were compared using a matching-adjusted indirect comparison (MAIC) of IsaPd from the ICARIA-MM study and PanVd from the PANORAMA-2 study (patients with RRMM who had received at least two prior treatments, including an immunomodulatory drug, and who had progressed on or within 60 days of their last Bortezomib-based therapy). The company included various potential or known prognostic factors and/or treatment effect modifiers as covariates in its MAIC model in order to re-weight the PFS data from the ICARIA-MM IsaPd arm to match the distribution of patient characteristics of the PanVd arm of the PANORAMA-2 study. The results appeared favourable to IsaPd with a HR of 0.369 (95% CI 0.259 to 0.526) for PFS, and a HR of 0.642 (95% CI: 0.38, 1.082) for OS.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The first key uncertainty relates to the open-label nature of the trial, which may have introduced measurement bias, and may have altered patterns of oral medication use by patients (e.g. oral pomalidomide, the relative dose intensity of which was higher in the Pd arm than in the IsaPd arm). The impact of this element of study design is difficult to assess; and its impact on the results of the study is unclear.

The second key uncertainty relates to the post-hoc analysis and reporting of patients in the ICARIA-MM study at 4L of treatment. The 4L population is directly relevant to the proposed positioning of

IsaPd within the treatment pathway, however the ERG has some reservations with this *post hoc* approach, as it was not a stratified group and does not have the protection of the randomisation when making comparisons between treatments.

A discrepancy between the arms in the use of subsequent daratumumab introduces uncertainty in the measurement of OS. Since subsequent daratumumab use (at 5L) is inconsistent with the current UK clinical management pathway for RRMM, this may compromise the generalisability of the ICARIA-MM study results to the UK context.

Within the MAIC it is not clear whether the covariates represent all relevant prognostic factors and/or treatment effect modifiers and the final comparison may be biased. Various survival models were fitted to the progression-free survival and OS data; however, the ERG has concerns with the modelling, including the way the treatment effect(s) were defined in the models, mixing baseline estimates from parametric models and estimates of treatment effects from Cox regression, and the use of hazards ratios from Cox regression models in survival models that are not proportional hazards models, and is not confident with making inferences from them.

1.4 Summary of the cost effectiveness evidence submitted by the company

Following the clarification process, the ERG believes the company's model to be generally well programmed and free from major errors. In its initial submission, the company's model was more complex and required several assumptions in order to explicitly distinguish between average time spent on and off 4L treatment. Whilst the model structure remained unaltered following the clarification process, the parameters were changed such that the model essentially was a standard partitioned survival model oncology approach using three-states (progression-free, progressed, and dead) with time on treatment modelled independently. Pivotal data for the comparison of IsaPd and Pd were taken from the ICARIA-MM study. For the comparison of IsaPd and PanVd, the company had to rely on a MAIC, which the company stated was exploratory and subject to limitations.

Within its base case analysis, the company maintained the use of estimated Patient Access Scheme prices (PASs) for pomalidomide, daratumumab and panobinostat; this is contrary to NICE guidance. The company did present results for its base case with the PAS discounts removed, which for ease of reading the ERG has termed the company's base case. The probabilistic results from this analysis indicated that IsaPd would generate an additional 1.055 quality-adjusted life years (QALYs) compared with Pd and an additional 0.791 QALYs compared with PanVd. These values result in an incremental cost-effectiveness ratio (ICERs) for IsaPd versus Pd of £130,321 per QALY gained and an ICER for IsaPd versus PanVd of £248,197 per QALY gained.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG identified seven limitations within the company's model and reporting of results. These were: i) identification of perceived modelling errors; ii) the time horizon is too short to capture all of the gains associated with IsaPd treatment; iii) the lack of comprehensive reporting of sensitivity analyses relating to the functions used for time-to-event data; iv) potentially inaccurate estimation of drug acquisition and administration costs; v) that drugs assumed to be used in 5L would not be used in the NHS in England; vi) potential face validity violations in the utilities sampled within the probabilistic sensitivity analyses; vii) and underestimation of uncertainty. The ERG explored the impact of amending some of these limitations; these did not markedly affect the ICER.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The clinical evidence for IsaPd for treating RRMM is based on a Phase III RCT (ICARIA-MM), which used a centralised computer-based method of allocation, and all outcomes reported on were pre-specified.

The mathematical model submitted following the clarification was largely appropriate for the decision problem. The company responded to the clarification questions raised and undertook the analyses requested.

1.6.2 Weaknesses and areas of uncertainty

The ICARIA-MM study used an open-label design, which may have impacted on measurements taken and also on patients' self-administration of pomalidomide.

Results for the population of interest, patients at 4L, were analysed and reported from the ICARIA-MM study post-hoc, which was not a stratified group and does not have the protection of the randomisation when making comparisons between treatments.

The OS results of the ICARIA-MM study may not be generalisable to England due to the differential subsequent use of daratumumab at 5L between the trial arms.

There was not a connected network of evidence to allow a more robust estimation of the relative clinical efficacy of IsaPd and PanVd.

Minor limitations were identified by the ERG in relation to the construction of the model and the presentation of the results.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG made two sets of changes to the company's base case to generate an ERG-preferred base case. Firstly, it corrected the perceived errors and secondly it extended the time horizon from fifteen to twenty years. The cumulative impact of these changes increased the probabilistic ICER for IsaPd versus with Pd to £133,461 per QALY gained and decreased the probabilistic ICER for IsaPd versus PanVd to £238,300 per QALY gained. Scenario analyses conducted by the ERG included: the use of alternative functions for OS data, time to treatment discontinuation data, and time to PFS data; assuming no drug wastage; and assuming 100% relative dose intensity for all 4L drugs. The range in the deterministic ICER when applying the sensitivity analyses to the ERG-preferred base case was £103,095 to £213,105 per QALY gained for IsaPd compared with Pd and £165,233 to £365,613 per QALY gained for IsaPd compared with PanVd. The lower value of the ranges are associated with an assumption of no drug wastage and the use of a jointly-fitted lognormal model with a treatment effect covariate for OS, whilst the upper value of the ranges is associated with the use of a jointly-fitted log-logistic model with a treatment effect covariate for TTD. If PanVd was a valid comparator then it was estimated that PanVd would dominate Pd, although the limitations of the MAIC need to be considered when evaluating this comparison.

These values presented in this report do not incorporate the commercial-in-confidence PAS discounts for interventions other than isatuximab; the results which include these discounts are contained in a confidential appendix to this report.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

Multiple myeloma (MM) is a malignant, haematopoietic tumour of plasma cells characterised by a clonal proliferation of bone marrow plasma cells.[1] Relapsed and refractory MM (RRMM) is defined as disease that becomes non-responsive whilst on treatment, or which progresses within 60 days of last therapy in patients who achieved at least a minimal response.[2] The company provide a comprehensive account of MM in terms of epidemiology, prognosis, and impact on patients' lives in Section B.1.3 of the company submission (CS).[3]

2.2 Critique of company's overview of current service provision

The CS[3] describes the clinical pathway for treating patients with MM and also indicates the proposed positioning of isatuximab, pomalidomide and low-dose dexamethasone (IsaPd) (reproduced as Figure 1). Whilst the company expects that the indication for isatuximab will be "*in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and proteasome inhibitor and have demonstrated disease progression on the last therapy*" the company anticipate that IsaPd will be used in patients who have received at least three prior lines of treatment, including lenalidomide, and would be used in fourth-line (4L). In line with recommendations from NICE those interventions within the Cancer Drugs Fund (CDF) were not considered comparators within this appraisal.

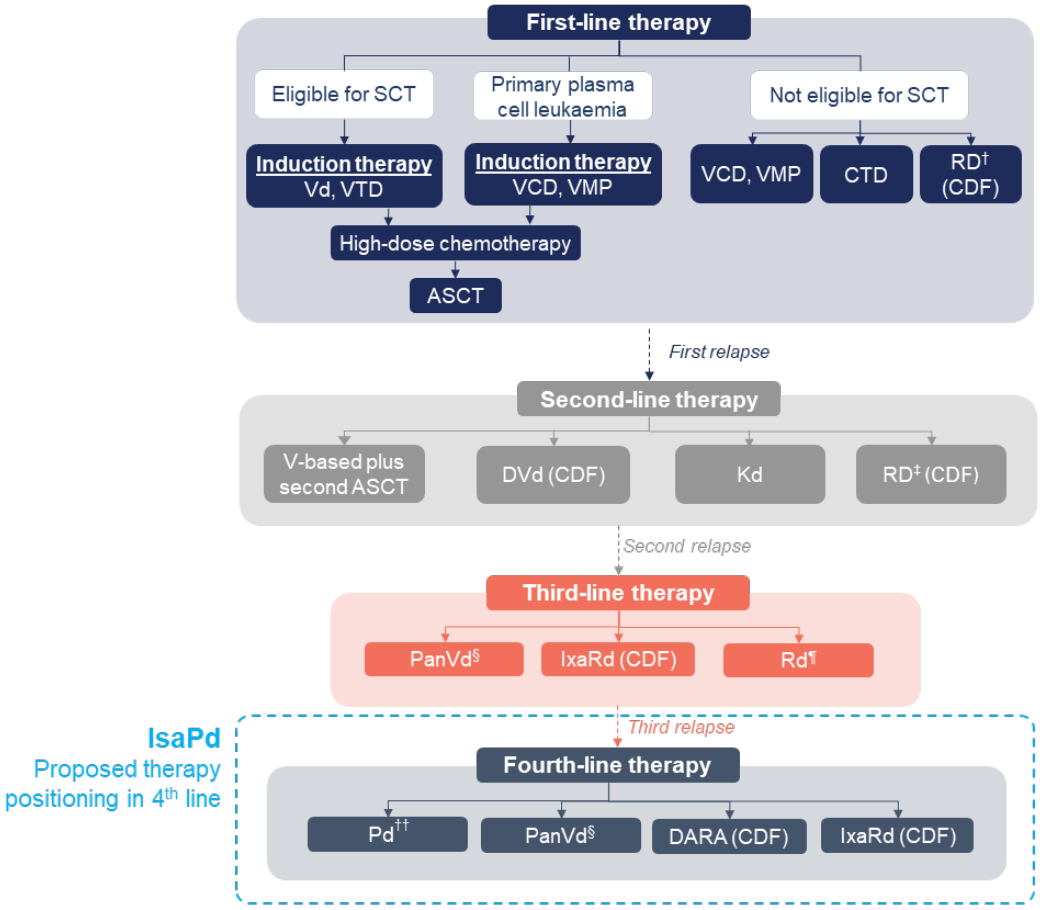
Clinical advice received by the ERG was broadly supportive of the company's description of the treatment pathway although the ERG's clinical advisors commented that: the pathway would be correct for those patients who are diagnosed now, however, patients currently at third-line (3L) or 4L may have had different preceding treatments; that treatments that are provided through the CDF (lenalidomide and dexamethasone; daratumumab, bortezomib with low-dose dexamethasone (DVd); and daratumumab monotherapy) are being widely used; and that it is possible for stem cell transplant to be used more than once. A stipulation for daratumumab monotherapy within the CDF was that it was used in 4L; as such, in the real-world setting Pd and panobinostat, bortezomib, and dexamethasone (PanVd) would be typically used at later lines. Daratumumab monotherapy is not a comparator in this appraisal as NICE does not allow drugs within the CDF to be comparators, leaving the comparators to IsaPd as Pd and PanVd.

Clinical opinion was divided on the frequency of use of PanVd in current practice although all noted the toxicity of the therapy. One clinician stated that PanVd is rarely used because of the toxicity of the regimen and perceived lack of response when other alternatives are available, whereas other experts

stated that PanVd was used in several units with dose or schedule adjustments used to manage toxicities.

Furthermore, clinical advice to the ERG anticipated that in the future the proportion of patients eligible for IsaPd is likely to decline due to the use of DVd in second-line or due to the use of daratumumab in combination with other agents at first-line, as patients who are refractory to an anti-CD38 agent were excluded from the ICARIA-MM randomised controlled trial (RCT).[4] However, clinicians stated that they would use IsaPd even in daratumumab-exposed patients provided they were not refractory to daratumumab in a prior line of therapy and had a non-anti-CD38-based treatment inbetween.

Figure 1: The company's diagram of the treatment pathway for people with MM and the proposed positioning of IsaPd



Source: adapted from NICE guideline on diagnosis and management of myeloma [NG35] [5]

Abbreviations: ASCT, autologous stem cell transplant; CDF, Cancer Drugs Fund; CTD, cyclophosphamide, thalidomide, dexamethasone; DARA, daratumumab monotherapy; DVd, daratumumab, bortezomib, low dose dexamethasone; IsaPd, isatuximab, pomalidomide, low dose dexamethasone; IxaRd, ixazomib, lenalidomide, low dose dexamethasone; kd, carfilzomib, low dose dexamethasone; PanVd, panobinostat, bortezomib, dexamethasone; PI, proteasome inhibitors; Pd, pomalidomide, low dose dexamethasone; Rd, lenalidomide, low-dose dexamethasone; RD, lenalidomide, dexamethasone; SCT, stem cell transplant; V, bortezomib; VCD, bortezomib, cyclophosphamide, dexamethasone; VD, bortezomib, low dose dexamethasone; VMP, bortezomib, melphalan, prednisone; VTD, bortezomib, thalidomide, dexamethasone;

†If lenalidomide is contra-indicated to/not tolerated by the patient and if the manufacturer provides lenalidomide according to the commercial agreement. ‡If patients have received only one previous therapy, which included bortezomib, and if the manufacturer provides lenalidomide according to the commercial agreement. §Panobinostat provided by the manufacturer at the discount agreed in the patient access scheme. ¶Drug cost of lenalidomide for patients who remain on treatment for more than 26 cycles must be met by the manufacturer. ††Pomalidomide provided by the manufacturer at the discount agreed in the patient access scheme.

2.3 Critique of company's definition of the decision problem

2.3.1 Population

The population within the company's base case is narrower than that specified within the NICE scope[6] in that the company have restricted IsaPd use to those at 4L. Supplementary analyses were

provided for patients who have only received two prior lines of therapy and for those at fourth-line or later.

2.3.2 Intervention

The intervention described in the CS is consistent with the final NICE scope,[6] which is the use of isatuximab, a humanised monoclonal antibody which binds to cell surface glycoprotein CD38, in combination with pomalidomide and dexamethasone. A regulatory submission for IsaPd was submitted to the European Medicines Agency (EMA) in April 2019 with a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) expected in early 2020, and regulatory approval expected in mid-2020. The expected indication has been described in Section 2.2.

IsaPd has three components each with different posologies. Isatuximab is infused at a dose of 10mg/kg weekly for four weeks, and then every two weeks, pomalidomide is taken orally for the first 21 days of each 28-day cycle, whilst dexamethasone (40mg, reduced to 20mg in patients aged 75 years or older) which can be administered intravenously or orally, is provided on the same days, in advance of isatuximab, to reduce the risk and severity of infusion reactions.

2.3.3 Comparators

The comparators listed in the final NICE scope[6] are pomalidomide and low-dose dexamethasone (Pd) and panobinostat, bortezomib and dexamethasone (PanVd). The company's base case focusses on Pd as the comparator, as it was stated that "*feedback from clinical experts during a Sanofi Advisory Board have indicated that this combination appears to be reserved for later line (i.e. ≥5th line) mainly due to its associated toxicities. This view is supported by market share data acquired by Sanofi. Similar views have been documented in previous NICE submissions (TA427, TA510).*" This position was not universally supported by the clinicians providing advice to the ERG. One clinician agreed with the company, but two believed that PanVd was used in several units with dose and schedule changes applied to manage toxicity. These clinicians stated that PanVd was typically used at 5L although this was due to NICE guidance for daratumumab monotherapy rather than for clear clinical reasons. Daratumumab monotherapy has been recommended for use in the CDF only at 4L, meaning that if clinicians wish to try multiple treatments including daratumumab monotherapy beyond 3L, that daratumumab monotherapy would be used at 4L, with Pd and PanVd being used at later lines. As NICE do not allow interventions on the CDF to be comparators in a single technology appraisal (STA), it was assumed that PanVd, where used, would be used at 4L for this decision problem, along with Pd.

Despite the company believing PanVd was not a comparator it undertook an exploratory analysis of IsaPd compared with PanVd "*in order to meet the requirements of the scope*" using a matching-

adjusted indirect comparison (MAIC) as IsaPd and PanVd were not part of a connected network of evidence.

The constituent parts of PanVd were assumed to be administered as follows: panobinostat (20mg) was assumed to be provided orally on six days across a three-week period, for a maximum of 48 weeks; bortezomib (1.3mg/m^2) was provided via injections on four days of a three-week period for the first 24 weeks, and then on two days of a three-week period for an additional 24 weeks. Dexamethasone was provided orally, at a dose of 20mg/day, eight times across a three-week period, for a maximum of 48 weeks.

2.3.4 Outcomes

The outcomes in the CS are in line with those in the final scope issued by NICE.[6] The company has also chosen to present results estimated within a mathematical model in terms of cost per life year gained (LYG).

2.3.5 Other relevant factors

A Patient Access Scheme (PAS) for isatuximab has been agreed with the Department of Health and Social Care; this takes the form of a simple discount of [redacted] of the list price, resulting in post-PAS costs of [redacted] for a 100mg vial and [redacted] for a 500mg vial. Pomalidomide and panobinostat, which are direct comparators at 4L, also have agreed simple PAS discounts in place; however, these are commercial-in-confidence. Lenalidomide, which could be used as a fifth-line (5L) treatment in the model also has a commercial-in-confidence PAS which is a simple discount. In line with the recommendation from NICE, all cost-effectiveness results presented in this document use the list prices for all drugs, except isatuximab, with an additional confidential appendix providing the results when the PAS for other interventions are applied.

3 CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the clinical effectiveness evidence contained within the CS[3] for IsaPd for treating RRMM. Section 3.1 provides a critique of the company's systematic review of clinical and safety evidence. Section 3.2 provides a summary of the clinical effectiveness and safety results together with a critique of the included study. Sections 3.3 to 3.5 present the indirect comparisons prepared by the company and additional work undertaken by the ERG. Section 3.6 provides the conclusions of the clinical effectiveness section.

3.1 Critique of the methods of review(s)

The company undertook a systematic literature review to identify all clinical evidence regarding the efficacy and safety of IsaPd and relevant comparators for the treatment of RRMM in adult patients who have received at least two lines of treatment. The systematic review methods for the clinical evidence are detailed in Section B.2.1 of the CS and CS Appendix D.[3]

3.1.1 Searches

The company performed one clinical effectiveness search to identify all clinical and safety studies of isatuximab and its comparators (bortezomib, carfilzomib, daratumumab, dexamethasone, elotuzumab, ixazomib, lenalidomide, melphalan panobinostat, pomalidomide, thalidomide, vorinostat, and bendamustine) for the treatment of RRMM in patients who have received at least two lines of treatment.

Several electronic bibliographic databases were initially searched covering the period from inception to October 2018; these were: MEDLINE and Epub Ahead of Print, In Process and & Other Non-Indexed Citations and Daily [via Ovid], Embase [via Ovid], Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials [via Wiley]), Health Technology Assessment database and Database of Abstracts of Reviews of Effects [via CRD], and several cancer/multiple myeloma conference proceedings websites (American Society of Clinical Oncology, European Society for Medical Oncology, European Haematology Association Congress, American Society of Hematology Annual Meeting, and the European School of Haematology International Conference on Multiple Myeloma). Updated database searches were carried out in June 2019.

The company searched two large clinical trials registers in June 2019 (clinicaltrials.gov and WHO ICTRP). Supplementary searches by the company include HTA and drug regulatory agency website searching (NICE, CADTH, Drugs@FDA, and EMA) (page 7 of Appendix D.1.1 of the CS).[3]

In Appendix D of the CS[3] (pages 7-30), the company reported the full and updated literature search strategies, all databases, trial registries, conference abstract and HTA and drug regulatory agency website searches. The ERG considers that the company's reported search strategies are comprehensive and would retrieve important citations relating to all eligible studies.

3.1.2 Inclusion criteria

The inclusion criteria are generally consistent with the NICE final scope,[6] with three inconsistencies: (1) in the company's systematic review inclusion criteria, there was no requirement for the population to have received lenalidomide and a proteasome inhibitor in a prior line of treatment; (2) the final NICE scope specifies pomalidomide in combination with low-dose dexamethasone and panobinostat in combination with bortezomib and dexamethasone, whereas the company's systematic review inclusion criteria lists additional medication (although the CS specifies that for the purposes of this submission, only IsaPd, Pd and PanVd were eligible for inclusion in the review); (3) the company's systematic review inclusion criteria list additional outcomes to the final NICE scope (time on treatment, treatment free interval, discontinuations, mortality). While not consistent with the stated decision problem, the ERG does not consider these differences to be problematic, as they would broaden rather than narrow the scope of the review, meaning that the relevant papers would still have been identified. Eligibility is restricted to English language publications, which introduces the risk that relevant data not published in the English language may have been missed by the review. It is difficult to estimate the impact of this, however the ERG does not anticipate that any important studies on IsaPd would have been published in another language and therefore missed.

3.1.3 Critique of study selection

Appendix D of the CS[3] states that two reviewers independently undertook record selection, with a third reviewer adjudicating any disagreements. The ERG considers this to be an appropriate and high-quality reviewing method. Full texts of all papers meeting the eligibility criteria in the abstract screening were obtained and screened against the eligibility criteria, although no detail is reported in the CS[3] about the number of reviewers who screened full texts for inclusion, or the process of decision-making. Consequently, the ERG cannot comment on this aspect of study selection. The ERG has screened the titles of the full texts excluded by the company (CS Appendix D, Table 3, page 51),[3] and has examined the full texts of any with potential relevance to the decision problem, and agrees with the exclusion of these texts. Neither the ERG nor clinical advisors to the ERG are aware of any additional studies within the scope of this appraisal.

The PRISMA flow diagram (CS, page 29) and text (CS, page 28)[3] referred to a total of three studies identified that were considered of relevance to the submission, one of which was presented in the PRISMA flow diagram as being 'additional evidence'. In response to clarification questions A1 and

A2,[7] the company stated that the three studies considered of relevance to the submission were ICARIA-MM, PANORAMA-1 and PANORAMA-2, and that the single-arm study presented as 'additional evidence', was PANORAMA-2 and was identified by the company rather than through the process of the systematic review, as the review focused on RCTs.[7] The PANORAMA-2 study was identified by the company reviewing other NICE submissions for RRMM (CS, Appendix K, page 280).[3]

3.1.4 Critique of data extraction

No detail is reported in the CS[3] about the process of data extraction, and thus it is not clear by whom this was done, if it was checked, how any disagreements were resolved, or which fields were extracted. The company's response to clarification question A3[7] indicates that two reviewers independently extracted data, with a third reviewer adjudicating any disagreements. The company's clarification response[7] outlines the fields extracted, and the ERG is satisfied that they are comprehensive.

3.1.5 Critique of quality assessment

The study quality of the ICARIA-MM RCT[4] was assessed using the checklist recommended by NICE for assessing the methodological quality of RCTs; this checklist bears a close resemblance to the Cochrane Risk of Bias tool,[8] which is widely regarded as the most robust tool for the assessment of bias in RCTs. Two reviewers independently assessed the risk of bias and any disagreements were resolved through discussion or by consulting a third reviewer. The ERG considers this to be a robust reviewing method.

No judgement on the overall risk of bias was reported in the CS, and no attempt has been made to integrate the quality assessment into the findings, or to consider the overall impact of the quality of the included study on the results.[3]

Quality assessment of the included study, ICARIA-MM, as undertaken by the company and the ERG, is presented in Section 3.2.3. A quality assessment of the PANORAMA-2 study[9] (see Section 3.2.1) is also presented in Section 3.3.1. The company did not provide a quality assessment of the PANORAMA-2 study in the CS; the ERG have undertaken this using the Newcastle-Ottawa Scale,[10] as it is an appropriate and validated quality assessment tool for non-randomised studies.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Studies included in/excluded from the submission

The CS[3] includes one study that examined the efficacy of IsaPd for treating RRMM – the ICARIA-MM RCT. ICARIA-MM is a pivotal prospective, open-label, multicentre, multinational, randomised parallel group double-arm Phase III study.[4] The CS and the clinical study report (CSR) state that ICARIA-MM was conducted across 102 sites in 24 countries: Australia, Belgium, Canada, Czechia, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Korea, New Zealand, Norway, Poland, Portugal, Russia, Slovakia, Spain, Sweden, Taiwan, Turkey, UK, and the USA.[3, 11] The number of patients and study centres in the UK is unclear. Forty-five (29.2%) and 45 (29.4%) patients in the IsaPd and Pd arms, respectively, were at 3L, 52 (33.8%) and 58 (37.9%) were at 4L, and 57 (37.0%) and 50 (32.7%) were at 5L+ (CS, Table 9, page 44). The additional study characteristics of ICARIA-MM are presented in the CS, Tables 6 and 7, pages 32 to 38.[3]

Two additional studies have supplied evidence for this appraisal. Study TCD14079 is a Phase 1b non-comparative open-label dose-escalation study, which was undertaken to determine the recommended dose of IsaPd in patients with RRMM. As a non-comparative Phase 1b study, the evidence within Study TCD14079 has been superseded by the ICARIA-MM study,[4] and therefore Study TCD14079 was not used to inform the company's economic model or indirect treatment comparison. However, it has been presented in CS Section B.2.8 (Table 26) and Appendix M.1 for completeness.[3]

The PANORAMA-2 study[9] is a single-arm Phase II study that assesses the safety and efficacy of PanVd, a comparator listed in the final NICE scope,[6] in patients with RRMM who had received at least two prior treatments. The PANORAMA-2 study has been used in the CS (Appendix K, Section K.4.1)[3] to inform the economic model and the indirect comparison with IsaPd (see Sections 3.3 and 3.4).

ICARIA-MM is used in the model for the key comparison of IsaPd vs Pd, whilst a MAIC using ICARIA-MM (IsaPd arm, intention to treat data) and PANORAMA-2 was done for the comparison of IsaPd against PanVd.

3.2.1.1 Patients

Eligibility criteria for the ICARIA-MM study are presented in Tables 6 and 7 of the CS,[3] pages 32 to 38. One key difference between the eligibility criteria for the ICARIA-MM study and the NICE final scope[6] is that patients were excluded from the ICARIA-MM study[4] if they had been treated with anti-CD38 monoclonal antibody and were refractory to this treatment. A clinical advisor to the ERG raised

the issue that this study would exclude any patient who had previously taken daratumumab at second line. Daratumumab (in combination with bortezomib and dexamethasone; DVd) is approved through the CDF for second-line treatment for MM. If DVd were to be routinely recommended as a treatment option in second-line, the implication of this exclusion criterion could mean that the ICARIA-MM study would not be directly relevant to future UK RRMM populations. Clinical advice to the ERG commented that IsaPd may be used in later lines post DVd despite both being anti-CD38 monoclonal antibodies, if the patient was not refractory to daratumumab and the patient had received a non-anti-CD38-based treatment inbetween.

A flow diagram of patient flow through the ICARIA-MM study is presented in Figure 12, page 39 of the CS,[3] which was correct at the time of data cut-off (although it is unclear whether this is the 11th of October or the 22nd November 2018; CSR, page 68).[11] Initially, 307 patients were randomised (IsaPd n=154; Pd n=153) and all but two patients in the IsaPd arm and four patients in the Pd arm received the treatment to which they had been allocated.[3] Of these, 100 patients (IsaPd n=65; Pd n=35) were still receiving ongoing treatment. Of the 154 patients who were randomised to IsaPd, 87 (56.5%) withdrew; in the majority of cases (n=66, 42.9%) this was due to disease progression (or death). Eleven (7.1%) withdrew because of adverse events (AEs), one (0.6%) due to poor compliance with the protocol, five (3.2%) due to patient choice and four (2.6%) due to other reasons. Of the 153 patients who were randomised to Pd (the control arm), 114 (74.5%) withdrew; in the majority of cases (n=88, 57.5%) this was due to disease progression (or death). Nineteen (12.4%) withdrew because of adverse events (AEs), six (3.9%) due to patient choice and one (0.7%) due to another reason. A *post hoc* analysis of patients at the fourth-line (4L) of treatment was conducted; there were n=52 patients at 4L in the IsaPd arm and n=58 patients at 4L in the Pd arm.[3]

Demographic and clinical characteristics were comparable between the IsaPd and Pd groups at baseline in both the ITT and 4L populations, with the following exceptions, which the CS notes (CS, Tables 8 and 9, pages 41 to 45): there was a greater proportion of patients aged ≥65 years in the IsaPd than the Pd arm (64.9% vs. 54.2%, respectively; 63.5% vs. 53.4% respectively in the 4L population); a greater proportion of males in the IsaPd than the Pd arm (57.8% vs. 45.8%, respectively; 57.7% vs. 46.6% respectively in the 4L population); and fewer patients from Western Europe in the IsaPd than the Pd arm (35.7% vs. 49.7%, respectively; 36.5% vs. 50.0% respectively in the 4L population), with a greater proportion of patients from Eastern Europe (18.2% vs. 13.1%, respectively; 25.0% vs. 17.2% respectively in the 4L population) and Asia (13.6% vs. 9.8%, respectively; 9.6% vs. 8.6% respectively in the 4L population). A slightly higher proportion of patients in the IsaPd than the Pd arm had impaired renal function at baseline (38.7% vs. 33.8%, respectively; 40.4% vs. 37.5% respectively in the 4L population). Clinical advice received by the ERG suggested that these slight imbalances were unlikely to have impacted on the relative effectiveness of IsaPd. A smaller proportion of patients in

the IsaPd than the Pd arm had high-risk chromosomal abnormalities (CA; 15.6% vs. 23.5%, respectively; 15.4% vs. 22.4% respectively in the 4L population); del(17p) and t(4;14) were the most frequent abnormalities. Clinical advice received by the ERG suggested that patients with high-risk CA tend to have a poorer prognosis, which may have been favourable to IsaPd. Although not discussed in the CS,[3] the ERG note that a smaller proportion of patients in the IsaPd than the Pd arm scored 0 on the Eastern Cooperative Oncology Group (ECOG) performance status measure at baseline (35.7% vs. 45.1%, respectively; 40.4% vs. 51.7% respectively in the 4L population), with a greater proportion of patients scoring 1 in the IsaPd arm than the Pd arm (53.9% vs. 44.4%, respectively; 48.1% vs. 39.7% respectively in the 4L population), which may have been unfavourable to IsaPd. The ERG notes that baseline balance or imbalance is not relevant if a characteristic is not prognostic. However, all stratification factors (i.e. age and lines of therapy) and known prognostic factors should be adjusted for in an analysis of covariance irrespective of baseline balance and their statistical significance. In the case of non-linear models, ignored covariates will produce biased estimates of treatment effect. The company has not generated estimates of treatment effect adjusted for stratification factors and known prognostic factors. Clinical advice received by the ERG suggested that the patient characteristics of the ICARIA-MM study (including the ITT and 4L populations) are broadly reflective of clinical practice in England, albeit being slightly younger and with a slightly lower proportion of black patients. The difference in the average age between patients in the ICARIA-MM study and in England may result in a different treatment effect, although the ERG is unable to comment on whether this would be less or greater for patients in England compared with that estimated in the trial. Clinical advisors to the ERG believed that the lower proportion of black patients would not affect the estimate of treatment efficacy.

3.2.1.2 Intervention

Patients in the IsaPd arm of the ICARIA-MM study received the following treatment combination: isatuximab 10mg/kg IV infusion on days 1, 8, 15 and 22 at Cycle 1, and then on Days 1 and 15 for subsequent cycles; pomalidomide 4mg orally on days 1 to 21 of each 28-day cycle; dexamethasone 40mg (or 20mg if the patient is aged ≥75 years old) orally or IV, on days 1, 8, 15 and 22 of each 28-day cycle. Dose reductions of isatuximab were not permitted, and none were reported (CS, Appendix G, page 118).[3] Permitted and disallowed concomitant treatments are detailed in the CS, Table 6, page 33. The company's clarification response to question A4[7] indicates that the majority (61.2%) of patients in the IsaPd arm of the ICARIA-MM trial received oral dexamethasone, 37.5% received dexamethasone both orally and IV, and 1.3% received dexamethasone via IV administration only. Around half of the 4L patients in the IsaPd arm (50.98%) received oral dexamethasone, 47.06% received both oral and IV dexamethasone, and 1.96% received dexamethasone via IV administration only.

There were [redacted] protocol deviations that were considered to be '*critical or major*' in the IsaPd arm before or during the ICARIA-MM study, and [redacted] in the Pd arm (CSR page 71)[11]. See Section 3.2.3.2 for further details.

3.2.1.3 Comparator

The comparator in the ICARIA-MM study was treatment with Pd, delivered in the following treatment combination: pomalidomide 4mg orally on days 1 to 21 of each 28-day cycle; dexamethasone 40mg (or 20mg if the patient is aged ≥75 years old) orally or IV, on days 1, 8, 15 and 22 of each 28-day cycle. This is identical to the pomalidomide and dexamethasone administration in the IsaPd arm and is consistent with current practice. The ERG considers this to be an appropriate comparator.[12] Permitted and disallowed concomitant treatments were the same as for the IsaPd arm, and are detailed in the CS, Table 6, page 33.[3] The company's clarification response to question A4[7] indicates that the majority (97.3%) of patients in the Pd arm of the ICARIA-MM trial received oral dexamethasone, with only 2.7% receiving dexamethasone both orally and IV; no patients in the Pd arm received dexamethasone via IV administration only. All 4L patients in the Pd arm received oral dexamethasone only.

3.2.1.4 Outcomes

Table 1 summarises the outcomes listed in the CS.[3] A small number of outcomes presented in the CS[3] were not included in the final NICE scope[6] and are not directly mentioned in the EMA's guideline on the evaluation of anticancer medicinal products.[3, 6, 12]

All efficacy and health-related quality of life (HRQoL) outcome data were analysed using the intention-to-treat (ITT) population, consisting of all randomised patients who gave written informed consent, regardless of whether they were treated or not, analysed according to the treatment group to which they were originally allocated.[3] Outcomes were also analysed *post hoc* within the 4L population, as IsaPd is positioned within the CS as a 4L treatment for RRMM. The company's clarification response question A5[7] indicates that the 4L *post hoc* analysis used data on patients at 4L from the ITT population (rather than the safety population).

Table 1: Summary of outcomes listed in the CS and their relationship to EMA research recommendations, the final NICE scope, and the company's health economic model

Outcome	Recommended by EMA for inclusion in Phase III trials?	In NICE scope?	Used in economic model?	Defined *a priori*?
Primary outcome				
Progression-free survival (PFS) – time from the date of randomisation to the date of first documentation of progressive disease or date of death from any cause	Y	Y	Y	Y
Secondary outcomes				
Overall response rate (ORR) from the date of randomisation to the date of first documentation of progressive disease (as defined by the IRC)	Y	Y	N	Y
Overall survival (OS) – time from the date of randomisation to the date of death from any cause	Y	Y	Y	Y
Time to progression (TTP) from the date of randomisation to the date of first documentation of progressive disease	Could be considered under "alternative endpoints" in the EMA recommendations	Y	Indirectly through PFS	Y
Duration of response (DOR) –from the first IRC determined response to first IRC determined disease progression or death	Could be considered under "alternative endpoints" in the EMA recommendations	Y	N	Y
Best overall response (BOR) – defined by IRC response assessment, from start of treatment until disease progression, death, initiation of further anti-myeloma treatment or cut-off date	Could be considered under ORR in the EMA recommendations	N	N	Y
Time to first response – from randomisation to first IRC determined response (partial response or better)	Could be considered under "alternative endpoints"	N	N	Added per SAP amendment 1
Time to best response –from randomisation to the first occurrence of IRC determined BOR (partial response or better)	Could be considered under "alternative endpoints" in the EMA recommendations	N	N	Y
HRQoL assessed by the electronic questionnaires EORTC-QLQ-C30, EORTC-QLQ-MY20 and EQ-5D-5L	Y	Y	Y (EQ-5D-5L was mapped to EQ-5D-3L)	Y
Treatment-emergent adverse events up to 30 days after last study treatment administration	Y	Y	Y	Y
Minimal residual disease – an exploratory endpoint to determine depth of response at the molecular level (see CSR, page 43)	N	N	N	Y
Time to next treatment	N	Y	Y	N

BOR - best overall response; DOR - duration of response; EMA - European Medicines Agency; EORTC-QLQ-C30 - European Organisation for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire with 30 items; EORTC-QLQ-MY20 - European Organisation for Research and Treatment of Cancer Quality of Life Multiple Myeloma Specific Module with 20 items; EQ-5D-5L – EuroQoL Group 5-dimention 5-Level questionnaire; HRQoL – Health-related quality of life; IMWG - International Myeloma Working Group; IRC - Independent Response Committee; ORR – Overall Response Rate; OS – Overall Survival; PFS – Progression-Free Survival.

Primary outcome

The primary outcome of the ICARIA-MM trial was PFS, assessed from the date of randomisation to the date of first documentation of progressive disease, as determined by the Independent Response Committee (IRC), according to the International Myeloma Working Group (IMWG) criteria using central laboratory results and central review of radiologic imaging, or the date of death from any cause, whichever came first.[3] While OS is arguably the most important outcome of a study, PFS is considered of benefit to patients and can be a feasible primary outcome in this context.[12] For the current appraisal, PFS data from the cut-off date (11th October 2018) were used. Patients without progressive disease or death before the analysis cut-off date were censored at the date of the last valid disease assessment.[11] Assessments were made on Day 1 of each cycle (every 4 weeks), and at the end of treatment (30 days after the last study treatment was administered).[11] The ICARIA-MM study was powered to detect a 40% reduction in the hazard rate between the study arms with 90% power using a one-sided significance level of 2.5%. Assuming an exponential distribution, this would occur when 162 PFS events had been observed.[4] The 162nd PFS event occurred on the 11th of October 2018; therefore, this date was used as the cut-off date for the efficacy analyses, which is the final data cut-off for PFS.[11] While the study was open-label, the CSR (page 30) reports that the IRC performed radiological and central laboratory assessments, on which the disease response evaluations were based, and the IRC was blinded to treatment allocation.[11]

Secondary outcomes

Outcomes listed in the final NICE scope[6] and reported in the CS[3] as secondary outcomes included:

- Overall survival (OS)
- Overall response rate (ORR)
- Time to progression (TTP)
- Duration of response (DOR)
- HRQoL
- Adverse events

Along with PFS, these outcomes form the focus of this report. Data on all other outcomes (see Table 1) are presented in the CS.[3]

EMA research recommendations advise that OS should be considered a secondary outcome in Phase III trials where PFS is the primary outcome, and should demonstrate or show a trend towards superiority.[12]

ORR was defined as the proportion of patients with stringent complete response, complete response, very good partial response and partial response as best overall response and assessed by the IRC using IMWG criteria. This is consistent with EMA recommendations that ORR be documented according to international standards.[12] The EMA also advises that the ITT principle be adhered to in evaluation of ORR. Data from the ITT and 4L populations of the ICARIA-MM study meet this recommendation, as all participants were analysed in the group to which they were allocated.[3] However, the 4L population is a *post hoc* non-stratified population that does not have the protection of the randomisation when making comparisons between treatments.

TTP and DOR might be considered among the "*alternative endpoints*" suggested by the EMA research recommendations[12] as acceptable, and Davis *et al.*[13] recommend TTP as a simple and comprehensive endpoint for Phase II to IV clinical studies of pharmaceutical agents. DOR was defined as the time from the date of the first IRC-determined response to the date of first IRC-determined disease progression or death, whichever occurred first.

HRQoL was assessed in the ICARIA-MM study by the use of the European Organisation for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire with 30 items (EORTC-QLQ-C30), European Organisation for Research and Treatment of Cancer Quality of Life Multiple Myeloma Specific Module with 20 items (EORTC-QLQ-MY20) and EuroQoL Group self-report questionnaire with 5 dimensions 5-level (EQ-5D-5L) questionnaires, prior to study-related activities on day 1 of each treatment cycle, at the end of treatment visit and 60 days (±5 days) after the last study treatment administration. According to clinical advice received by the ERG, such measures would not be routinely used in clinical practice (HRQoL would not be formally measured in real-world practice). However, the EORTC-QLQ-C30 is a commonly-used questionnaire for research with myeloma patients. The results for the cognitive, social and emotional functioning subscales were not in the CS; the company have submitted these in their response to clarification question A11.[7] Clinical advice received by the ERG suggested that the global health status (GHS) may not be a reliable indicator of perceived health/HRQoL as people find it difficult to consider their health and wellbeing in such global terms, that perceived health varies over the course of RRMM and that there could be high unmet needs. The EMA research recommendations[12] and EMA guidance on measuring HRQoL in oncology[14] recommend the use of a validated cancer-specific HRQoL measure where possible (although they do not specify which instrument should be used), and as such, the EORTC-QLQ-C30 fulfils this criterion.

All adverse events (AEs) reported in the ICARIA-MM study were classified as treatment-emergent adverse events (TEAEs) and were recorded from the time of informed consent to 30 days following the last administration of IsaPd or Pd.[3] These were defined as AEs that "*developed, worsened*

(according to the investigator opinion) or became serious during the TEAE period" (CSR, page 44).[11] The method of measuring AEs was not given in the CS,[3] although the CSR (page 44)[11] reported that all AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. According to the CS (page 46),[3] the safety population consisted of all patients from the ITT population who received at least one dose or part-dose of their randomised treatment (IsaPd or Pd). Patients were analysed according to the treatment group to which they were originally allocated.[3] No definition of what constituted a serious adverse event (SAE) is presented in the CS[3] or CSR.[11] However, the clinicaltrials.gov record states that an SAE constituted "*any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a medically important event*".[15]

3.2.1.5 Study design

The ICARIA-MM study was a prospective, open-label, multi-centre, multinational, parallel-group Phase III RCT, where eligible patients (n=307) were randomised to IsaPd or Pd. Patients were randomised at a 1:1 ratio using an interactive response technology (IRT) system. Randomisation was stratified by age (<75 years vs. ≥75 years) and number of previous lines of therapy (2 or 3 vs. >3) (CS, Table 6, page 32).[3] The ERG considers that the study design could have been more rigorous, as the ICARIA-MM trial was open-label and the EMA evaluation guidelines[12] recommend the use of double-blind Phase III RCTs that compare against the current standard of care for establishing the benefit-risk profile of a medicinal product.

Post hoc analyses were conducted and reported in the CS for a subgroup of patients in the ICARIA-MM study at 4L of treatment, relating to selected outcomes.[3] The ERG's appraisal focuses on evidence from the 4L *post hoc* analyses, as this is the most relevant patient population from the ICARIA-MM study based on the proposed positioning by the company and these data have informed the company's health economic model. However, the ERG has some reservations with this *post hoc* approach, as it was not a stratified group and does not have the protection of the randomisation when making comparisons between treatments.[16] The selection of the *post hoc* population was based on consideration of the proposed position of IsaPd in the RRMM treatment pathway. However, as baseline demographics and clinical characteristics were similar between the 4L patients and the full population and clinicians did not believe the relative efficacy to differ by line of treatment the analyses were believed suitable for decision making.

3.2.1.6 Ongoing studies

The ICARIA-MM study is currently ongoing, with efficacy data from the 11th of October 2018 cut-off and safety data from the 22nd of November 2018 cut-off used in the CS.[3] The PFS data from the

ICARIA-MM study were mature. However, OS data are less mature. The final analysis of OS will occur after ≥220 deaths have been observed, which is expected in Q2 2021 (CS, page 91).[3]

An additional study, the IKEMA study, is reported in the CS (page 87)[3] as being currently ongoing. However, as the study compares isatuximab, carfilzomib and dexamethasone with carfilzomib and dexamethasone in patients with RRMM, the ERG does not consider this relevant to the current decision problem.

3.2.2 Details of relevant studies not included in the submission

The ERG is confident that the ICARIA-MM study is the only relevant study in this patient population, that the PANORAMA-1[17, 18] and PANORAMA-2[9] studies are potentially the only relevant comparator studies for the comparison with IsaPd to PanVd (see Section 3.3), and that no relevant studies have been omitted from the CS.[3] The methods employed by the company and a critique of these methods are provided in Section 3.4.

3.2.3 Summary and critique of the company's quality assessment

3.2.3.1 Critical appraisal of study quality of ICARIA-MM

The company provided a critical appraisal of the validity of the ICARIA-MM study[4] using the checklist recommended by NICE, which bears a close resemblance to the Cochrane Risk of Bias tool.[19] A summary of the risk of bias in the ICARIA-MM study undertaken by the company alongside the ERG's independent quality assessment is presented in Table 2. The ERG has also specified the level of risk of bias for each criterion.

The company's critical appraisal and the ERG's critical appraisal of the ICARIA-MM study[4] were similar. The ERG concludes that there is a moderate risk of bias for the ICARIA-MM study; the company did not provide a summary appraisal of risk of bias. Both the company and the ERG agree that there were some differences in baseline characteristics between study arms, although the relevance of these depends on whether the characteristics are prognostic; a correct analysis includes all stratification factors and all observed prognostic variables irrespective of baseline balance. The study was open-label, which may have introduced measurement bias; and a greater proportion of patients in the Pd group than the IsaPd group withdrew due to disease progression (whether this was expected or not was unclear from the CS).[3]

Details of the PANORAMA-2 study quality assessment are reported in Section 3.3.

Table 2: Company and ERG quality assessment of ICARIA-MM (adapted from CS, Appendix K, Table 46)

Quality assessment criterion question	Company quality assessment (yes/no/not clear/NA)		ERG quality assessment (yes/no/not clear/NA)	
	Grade	Explanation	Grade	Explanation
Was randomisation carried out appropriately?	Yes	Patients were randomised according to an interactive response system and stratified according to age and prior therapy.	Yes	Patients were randomised using an IRT system, stratified by age and previous lines of therapy.
Was the concealment of treatment allocation adequate?	Yes	A centralised interactive response system was used to allocate patients.	Yes	Patients were allocated using a centralised IRT system.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Unclear	Authors stated that the baseline characteristics of the two groups were generally well balanced with the exception of gender and geographical region, but no statistical analysis conducted.	Unclear	Baseline characteristics differed on some demographic and disease-related characteristics.
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	Open-label. Disease response assessments were evaluated based on radiological and central laboratory assessments by the IRC which was blinded to treatment group allocation.	No	The study was open-label. The IRC (which was blinded to treatment allocation) undertook the radiological and central laboratory assessments, on which the disease response evaluations were based.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Unclear	Higher rate of discontinuation due to disease progression in the Pd group: 57.5% vs 42.9% in the IsaPd group.	Unclear	A greater proportion of patients in the Pd group (57.5%) than in the IsaPd group (42.9%) withdrew due to disease progression. It is unclear whether this was unexpected or not, although this was explained in terms of the efficacy of IsaPd.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	There was no evidence of selective reporting. All specified outcomes were reported.	No	There are no outcome measures specified in the protocol (including previous versions) that have not been reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The ITT analysis was reported and included all patients randomised for efficacy outcomes. Details of patient censoring also provided.	Yes	Analysis using the ITT population was reported for all efficacy outcomes, and this included all randomised patients.

IRC – Independent Response Committee; IRT – interactive response technology; ITT – intention to treat;

3.2.3.2 Protocol deviations

The CSR[11] reports a total of [redacted] critical or major protocol deviations in the IsaPd arm and [redacted] in the Pd arm. A comparable proportion of patients in the Pd arm than the IsaPd arm ([redacted] vs. [redacted]) had progressed after 60 days of the last dose of the immediate previous line/regimen. [redacted] in the IsaPd arm ([redacted]) had prior exposure to pomalidomide and [redacted] in the IsaPd arm ([redacted]) had been diagnosed or treated for another malignancy within three years prior to randomisation. In the Pd arm, [redacted] had an absolute neutrophil count < 900, [redacted] had a major procedure or major surgery within 14 days prior to study initiation, [redacted], and [redacted] did not have evidence of measurable disease (M-protein in serum < 0.5g/dL and urine < 200mg/24 hours). The ERG considers these protocol deviations unlikely to impact on the conclusions of the ICARIA-MM study.

Another consideration is the difference in pomalidomide exposure between the IsaPd and Pd arms, which may impact on trial outcomes. The mean relative dose intensity (RDI) of pomalidomide was [redacted] (SD [redacted]) in the IsaPd arm, and [redacted] (SD [redacted]) in the Pd arm (CSR, Table 45, page 131).[11] As ICARIA-MM was open-label and pomalidomide was taken orally, it is possible that patients in the Pd arm took a higher dose of pomalidomide to compensate for not receiving isatuximab.

3.2.4 Summary and critique of results

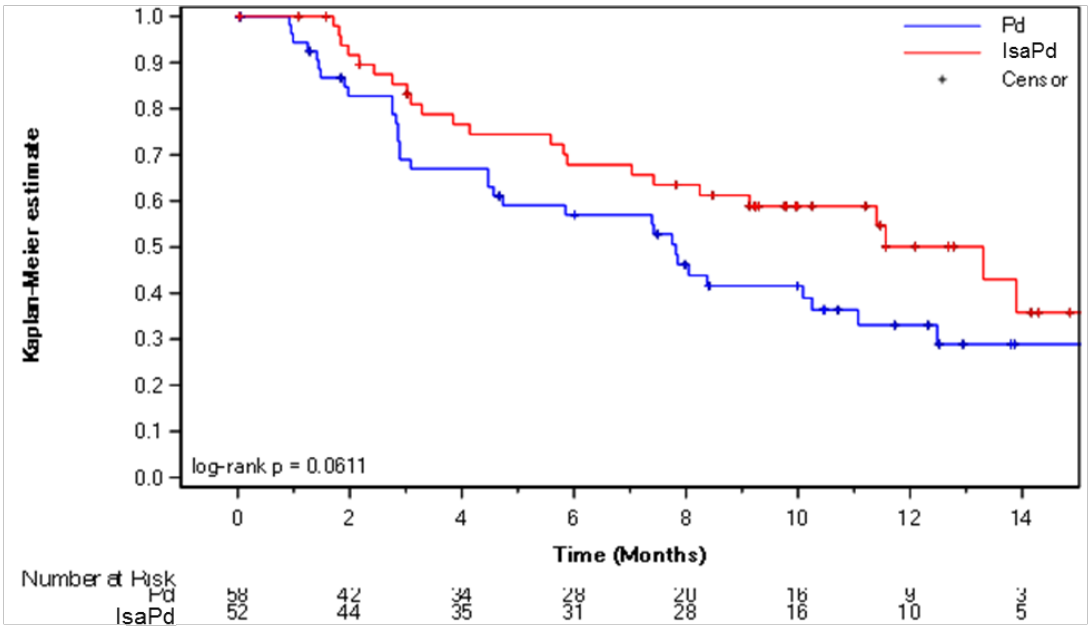
The data cut-off date for the efficacy analyses was the 11th of October 2018, and the cut-off date for other analyses (safety, disposition, and baseline characteristics) was the 22nd of November 2018. As the 162nd PFS event occurred on 11 October 2018, this date was used as the cut-off date for the efficacy analyses and a last patient visit of 22 November 2018 was selected (CSR, page 68).[11] The median duration of follow-up was reported in the CS as being 11.56 and 11.73 (for OS) (CS, page 57), and the recently published Attal *et al*. paper gives the median duration of follow-up as being 11.6 months (IQR 10.1-13.9) at data cut-off for the efficacy analyses among the trial population.[4] The mean (SD) duration of exposure was 37.81 (20.29) and 29.33 (20.57) weeks for the IsaPd and Pd arms, respectively, and the median (range) duration of exposure was 41.00 (1.3, 76.7) and 24.00 (1.0, 73.7) weeks for the IsaPd and Pd arms, respectively.

3.2.4.1 PFS (primary endpoint)

PFS was assessed after 162 patients (of 309) had progressed or died, which included 56 PFS events in the 4L population (n=110). In the 4L population, the median PFS was greater in the IsaPd arm (13.31 months [95% CI: 7.425, not calculable]) than in the Pd arm (7.82 [95% CI:

4.468, 11.072]) (stratified (by age) Log-Rank test *p*-value vs Pd: 0.0611), and the stratified (by age) hazard ratio (HR) was 0.598 (95%: CI 0.348, 1.030), which the CS states represents a 40.2% risk reduction of disease progression or death in favour of IsaPd compared with Pd (Figure 2).[3] Twenty-nine (55.8%) and 25 (43.1%) of 4L population patients in the IsaPd and Pd arms, respectively, had not had a PFS event at data cut-off.

Figure 2: Kaplan-Meier curves for PFS by treatment group, 4L population (adapted from CS, Figure 14, page 53)



Cut-off date: 11th October 2018.

Log-rank p-value stratified by age (<75 years vs ≥75 years) according to IRT. One-sided significance level: 0.025.

Abbreviations: IRT, interactive response technology; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ITT, intention-to-treat; MM, multiple myeloma; Pd, pomalidomide, low-dose dexamethasone; PFS, progression free survival.

3.2.4.2 ORR

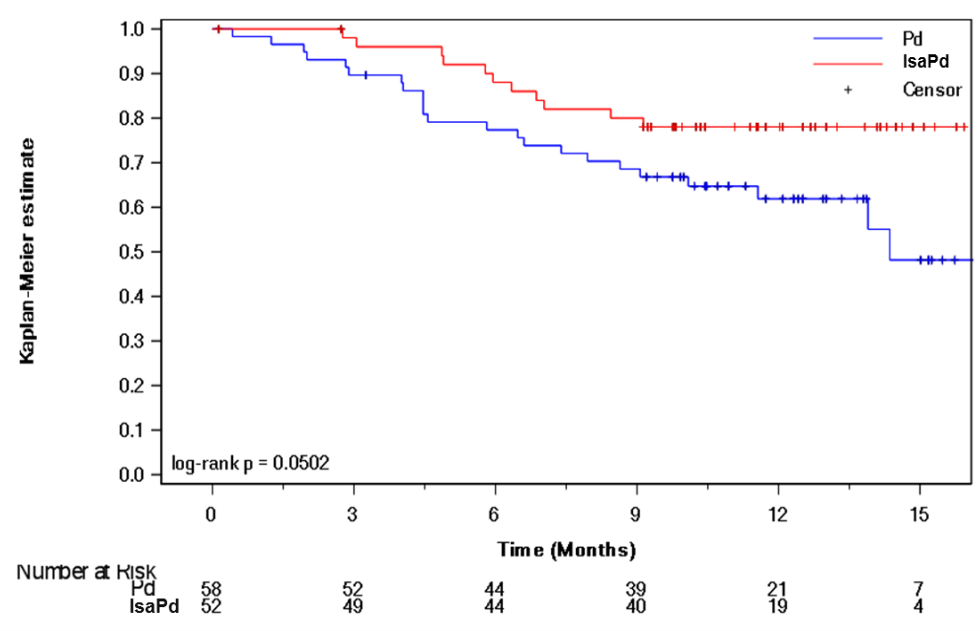
The ORR for patients in the 4L population was higher in the IsaPd arm (53.8%) than in the Pd arm (46.6%), although this difference was not statistically significant (*p*=0.3991). Similarly, a (non-statistically significantly) greater proportion of participants in the IsaPd arm had a very good partial response or better (26.9% vs. 15.5%; *p*=0.1552, for the IsaPd and Pd arms, respectively) and a complete response (3.4% vs. 1.9% for the IsaPd and Pd arms, respectively (*p*-value not reported). The CS states that "*the proportion of patients with CR in the IsaPd was likely to be underestimated; isatuximab interferes with M-protein measurements in the immunofixation test*" and thus it was possible that some patients recorded as having a near-complete response (i.e. a response on all measures except the immunofixation test) may have in fact had a complete

response. Clinical advice received by the ERG suggested that this was possible, although this phenomenon would be unlikely to have a clinically relevant impact on this outcome variable. Data for the ITT population of ICARIA-MM are reported in the CS, (pages 54-55).[3]

3.2.4.3 OS

Interim data and analyses were reported in the CS for OS. The interim analysis of OS for IsaPd and Pd was conducted using a log-rank test, with a one-side significance level of 0.0008 (determined by using O'Brien and Fleming α-spending function) (CS, page 57). Among the ITT population, 99 death events (43 in the IsaPd arm and 56 in the Pd arm) were reported at data cut-off; this represented 45% of the target of 220 events required to achieve 80% statistical power to detect a 31.5% reduction in hazards at a one-sided significance level of 2.5%. Final OS analyses are planned once 220 deaths have been observed (anticipated in Q2 2021). In the 4L population, there were 34 death events; 11 (21.2%) in the IsaPd arm and 23 (39.7%) in the Pd arm at data cut-off; 69% of 4L patients were still alive at a median follow-up of 11.6 months and were censored. A trend for greater median OS in the IsaPd arm (compared with the Pd arm) was reported in the CS, with a median OS of 14.36 months (95%: CI 11.57, not calculable) in the Pd arm whilst the median OS had not been reached in the IsaPd arm (stratified HR 0.49 [95% CI 0.24, 1.02], p=0.0502) (Figure 3; CS, pages 60-61).

Figure 3: Kaplan-Meier curves for OS† by treatment group, 4L population (adapted from CS, Figure 16, page 62)



†Cut-off date: 11th October 2018.
Log-rank p-value stratified by age (<75 years vs ≥75 years) according to IRT. One-sided significance level: 0.025.
Abbreviations: IRT, interactive response technology; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ITT, intention-to-treat; MM, multiple myeloma; OS, overall survival; Pd, pomalidomide, low-dose dexamethasone

OS may have been impacted by the subsequent use of daratumumab which does not reflect current clinical pathways in England. The CS[3] reported that 3.8% and 27.6% of 4L patients in the IsaPd and Pd arms, respectively, had received daratumumab as subsequent therapy at the cut-off date, which increased to values of 7.1% and 38.1% given longer follow-up to July 2019 (Sanofi, data on file)). Subsequent use of daratumumab in patients who progress at 4L will potentially be inconsistent with the current clinical management pathway for RRMM in England if isatuximab is approved for use at 4L. Therefore, this may compromise the generalisability of the ICARIA-MM study results to the context of the NHS in England. The CS urges caution in interpreting the longer-term OS data, considering the high levels of censoring and subsequent therapy, particularly daratumumab.[3]

3.2.4.4 TTP

The median TTP was greater in the IsaPd arm of the 4L population (13.31 months [95% CI: 8.25, not calculable]) compared with the Pd arm (8.05 months [95% CI: 5.85, not calculable]; HR and *p*-value not reported). Median TTP for the ITT population is reported in the CS, Table 20.[3]

3.2.4.5 DOR

The median DOR was not calculable for both the IsaPd and Pd arms in the 4L population. Although the stratified HR (0.63 [95% CI: 0.22, 1.77]; *p*-value not reported) favoured IsaPd over Pd there was uncertainty regarding the direction and magnitude of effect. Median DOR and stratified HR for the ITT population is reported in the CS, Table 20.[3]

3.2.4.6 HRQoL

Among the 4L patients, HRQoL assessed using the EQ-5D-5L health state utility index and visual analogue scale was similar between groups and worsened slightly over time, although slightly more so in the IsaPd arm than the Pd arm. The company urge caution in interpreting the results due to a small sample size and absence of significance testing (CS, page 74).

There was little difference between IsaPd and Pd in the 4L population on EORTC QLQ-C30 score (representing scores in physical functioning, role functioning, cognitive functioning, emotional functioning and social functioning subscales) across the treatment cycles, with both treatments having a reduced HRQoL at the end of treatment, presumably due to disease progression (CS, Figure 18, page 72).[3] The company have submitted results for the cognitive, social and emotional functioning subscales in their response to clarification question A11,[7] and the results are similar for these subscales.

Results from the QLQ-MY20 were not reported for the 4L population. For the ITT population, the CS reports that there was no clinically meaningful change from baseline in the body image, future perspective, disease symptoms, and side effects scores (page 71).

3.2.4.7 Safety and tolerability

IsaPd appears to be generally well tolerated. At 4L, a greater proportion of patients in the IsaPd arm than the Pd arm experienced grade ≥3 TEAEs (84.3% vs 69.0%, respectively) and treatment-emergent serious adverse events (64.7% vs 53.4%, respectively). However, fewer 4L patients in the IsaPd than the Pd arm had fatal events (7.8% vs 8.6%, respectively) or discontinued treatment due to a TEAE (7.2% vs 17.2%, respectively). An overview of TEAE rates in the 4L population is provided in the CS, Table 28, and rates of specific TEAEs by system organ class for the safety population are provided in the CS, Table 30.[3]

3.2.4.8 Subgroups

The company proposes that IsaPd would be used as a 4L treatment, which represents a known subgroup of the broader marketing authorisation. As such, the company has provided data on this subgroup. Further discussion on subgroups are provided in Sections B2.6.1 and B2.7 of the CS. It is reported that "*Pre-specified subgroup analyses demonstrated a positive treatment effect with IsaPd vs Pd (HR values ranging from 0.479 to 0.827) in all subgroups considered, consistent with the overall PFS analysis. In addition, the analyses showed no significant interaction at the 10% alpha level for treatment arms vs stratification factors, treatment arms vs demographic characteristics, or treatment arms vs patients' baseline characteristics, indicating an overall consistent treatment effect across those subgroups.*"[3]

The company performed subgroup analyses with respect to 12 potential prognostic factors and/or treatment effect modifiers in addition to subgroup analyses of the two stratification factors (age and lines of therapy). Although this approach to assessing differential treatment effects is common, it does have limitations: assessing treatments effects of a subgroup assumes there is no residual heterogeneity of treatment effect within the subgroup; when treatment interacts with factors not used in forming the subgroups, or when the subgrouping variable interacts with an omitted factor, the subgroup treatment effect may be misleading; constructing subgroups from a factor that is continuous assumes that there is a discontinuous treatment effect at the cut-off(s), which is unrealistic. Assessing differential treatment effects is best done through formal interactions tests. As before, the ERG notes that all stratification factors and known prognostic factors should be adjusted for in an analysis of covariance irrespective of baseline balance and their statistical significance, and that unadjusted estimate of treatment effect are biased. The company's approach to estimating the effect of individual covariates should have simultaneously adjusted for stratification factors. Furthermore, the company summarised the results of their subgroup analysis by providing the minimum and maximum hazard ratios but did

not include confidence intervals for them. Nevertheless, in spite of the claim by the company that the hazard ratios for the effect of treatment in all subgroups was consistent with the overall PFS analysis, the actual estimates were quite different. The impact of this on absolute estimates of PFS for patients treated with IsaPd would depend on the risk of PFS for patients treated with Pd.

In addition, the company conducted a multivariable analysis and identified variables to include in the multivariable regression model using stepwise methods. The ERG has concerns with the use of stepwise methods, including: R^2 values are biased upwards, F statistics do not have the claimed distribution, standard errors of parameter estimates are too small, p-values are too low because of multiple comparisons and it is not clear how they should be adjusted, parameter estimates are biased away from the null value, and collinearity problems are exacerbated. Furthermore, the approach used by the company failed to take account of what is already known, including that age and lines of therapy are prognostic factors. In clarification question A13,[7] the ERG asked the company to re-run the multivariable regression analysis leaving in the model the stratification factors and any known prognostic factors irrespective of their statistical significance and baseline balance; to include other potential prognostic factors using criteria other than simply statistical significance, including the magnitude of effect and expert opinion; and to include covariates that are continuous variables (such as age) as continuous variables and assess their relevance using appropriate non-linear relationships. In response, the company simply provided a model with all covariates included and did not assess any potential differential treatment effects (Response to clarification questions,[7] Table 6). Although, as expected, the adjusted treatment effect is greater than the unadjusted treatment effect, it is not clear whether a reduced model would be more appropriate or if interaction terms with treatment should be included.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The PANORAMA-2 study[9] is a single-arm Phase II study that assesses the safety and efficacy of PanVd, a comparator listed in the final NICE scope,[6] in patients with RRMM who had received at least two prior treatments. The PANORAMA-2 study has been used in the CS (Appendix K, Section K.4.1) to inform the comparison of IsaPd against PanVd (see Section 3.1.6) using a MAIC. While the inclusion criteria based on the number of lines was comparable in PANORAMA- 2 and ICARIA-MM, this was not the same as the target population (4L). Patients were adults with relapsed and bortezomib-refractory MM who had received at least two prior lines of therapy (median 4 prior lines, range 2-11).[9] The treatment schedule and baseline characteristics are reported in the Richardson *et al.* publication,[9] and the baseline characteristics of the ICARIA-MM and PANORAMA-2 studies are compared in Table 3.

Table 3: Comparison of baseline characteristics of ICARIA-MM and PANORAMA-2 (adapted from CS, Appendix K, Table 42, page 286)

Characteristic	ICARIA-MM[4]		PANORAMA-2[9]
	IsaPd (n=154)	Pd (n=153)	PanVd (n=55)
Median age (range), years	68 (36 to 83)	66 (41 to 86)	61(41 to 88)
Gender n (%) male	89 (57.8)	70 (45.8)	29 (52.7)
Ethnicity n (%)	White: 118 (76.6) Asian: 12 (13.6) Black or African American: 1 (0.6) Native Hawaiian or other pacific island: 2 (1.3) Unknown: 12 (7.8)	White: 126 (82.4) Asian: (15 (9.8) Black or African American: 3 (2) Native Hawaiian or other pacific island: 1 (0.7) Unknown: 8 (5.2)	NR
Mean weight (SD or range), kg	NR	NR	NR
ECOG performance status n (%)	ECOG 0: 55 (35.7) ECOG 1: 83 (53.9) ECOG 2: 16 (10.4)	ECOG 0: 69 (45.1) ECOG 1: 68 (44.4) ECOG 2: 16 (10.5)	ECOG 0: 26 (47.3) ECOG 1: 25 (45.5) ECOG 2: 4 (7.3)
Time since diagnosis Median years (range)	4.5 (0.6- 18.4)	4.1 (0.5- 20.5)	4.56 (0.6 to 22.0)
ISS disease stage n (%)	I: 36 (23.4)) II: 49 (31.8) III: 42 (27.3) Unknown: 27 (17.5)	I: 41 (26.8) II: 48 (31.4) III: 44 (28.8)) Unknown: 20 (13.2)	I: 18 (32.7) II: 23 (41.8) III: 13 (23.6) Missing: 1 (1.8)
Cytogenetic features n (%)	Del17p, t(4;14) or t(14;16) Absent: 80 (52.3) Present: 33 (21.6) Unknown: 33 (21.6)	Del17p, t(4;14) or t(14;16) Absent: 80 (52.3) Present: 33 (21.6) Unknown: 33 (21.6)	FISH, n (%) Normal: 2 (3.6) Any abnormality: 35 (63.6) del17p, t(4;14), or t(14;16): 14 (25.5) del13q: 5 (9.1)

Characteristic	ICARIA-MM[4]		PANORAMA-2[9]
	IsaPd (n=154)	Pd (n=153)	PanVd (n=55)
			t(11;14): 14 (25.5) 3+: 1 (1.8)
Lab tests Serum LDH levels Albumin levels Renal function (creatinine levels [mL/min]))	 ≤ULN: 106 (68.8) NR	 ≤ULN: 1062 (66.7) NR	 NR Median: 3.69 g/L (30.6 to 48.9) NR
Number of prior therapies Median (range)	3 (2 to 11)	3 (2 to 10)	4 (2 to 11)
Prior autologous stem cell transplant n (%)	83 (53.9)[a]	90 (58.8)[a]	31 (56.4)[b]
Refractory to lenalidomide n (%)	144 (93.5)[c]	140 (91.5)[c]	Not identified by the ERG

[a] *Data from ICARIA-MM CSR (Table 21, page 86)*[11]
[b] *Data from Richardson et al. 2013*[9]
[c] *Data from CS (Table 9, page 44)*[3]
Abbreviations: ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; Isa-Pd, isatuximab+ pomalidomide+ dexamethasone; ISS, International Staging System; LDH, lactate dehydrogenase; NR, not reported; PanVd, panobinostat+ bortezomib+ dexamethasone; Pd, pomalidomide+ dexamethasone; SD, standard deviation

3.3.1 Critical appraisal of study quality of PANORAMA-2

Table 4 presents the quality assessment of the PANORAMA-2 study[9] undertaken by the ERG, based on the Newcastle-Ottawa scale.[10] No quality assessment of the PANORAMA-2 study was presented in the CS.[3]

Table 4: ERG quality assessment for PANORAMA-2 using the Newcastle-Ottawa Scale

Quality assessment question	ERG's quality assessment
Representativeness of the exposed cohort	Unclear
Selection of the non-exposed cohort	N/A (single-arm study)
Ascertainment of exposure	Patients were administered panobinostat, bortezomib and dexamethasone as a study treatment intervention. Administration was monitored.
Demonstration that outcome of interest was not present at start of study	The primary outcome was overall response rate, which could not have been present at baseline.
Comparability of cohorts on the basis of the design or analysis	N/A
Assessment of outcome	Standard clinician-assessed outcome measurements were used, open-label
Was follow-up long enough for outcomes to occur?	Patients were assessed for up to two years, which is sufficient for outcomes to occur
Adequacy of follow up of cohorts	Seven of the 55 patients entered phase 2 of treatment and remained on treatment at the data cut-off. Discontinuations and withdrawals were accounted for; however, attrition was high.
Stars total	**3**

The ERG has rated the PANORAMA-2 study[9] moderate to poor in terms of study quality. The main source of bias is the unblinded nature of the outcome assessment.

3.4 Description and critique of the indirect comparison and/or multiple treatment comparison

The company undertook an exploratory analysis of IsaPd compared with PanVd "*in order to meet the requirements of the scope*" using a MAIC as IsaPd and PanVd were not part of a connected network of evidence.

Initially, the company assessed whether it was feasible to perform a network meta-analysis (NMA) depending on the similarity of the studies in each network against the following criteria: the quality of the methods employed in conducting randomised trials; confounding factors in relation to participant populations; confounding factors in relation to circumstances, and similarity of treatments (common reference and interventions).

The company defined the following outcomes as treatment effect modifiers: age; sex; ethnicity; weight; stage or duration of disease; ECOG performance score; cytogenetic risk group; co-existing disease and concomitant treatments; prior therapies; location; setting; and date of studies.

Three studies were considered relevant with respect to this comparison: ICARIA-MM,[4] PANORAMA-1,[20] and PANORAMA-2.[9] ICARIA-MM compared IsaPd against Pd in adult patients who had received at least 2 prior lines of treatment. PANORAMA-1 compared PanVd against placebo in patients who had received 1-3 prior lines of treatment, although data from the subgroup of patients who had received 2 prior lines of treatment was available. PANORAMA-2 was a single arm study of PanVd in patients who received 2 or more prior lines of treatment. Hence, the studies did not form a network of evidence.

The company assessed the consistency of the PanVd PFS data across the PANORAMA-1 and PANORAMA-2 studies using the Kaplan-Meier (KM) estimates at 6 and 12 months, estimating the HR from a Cox proportional hazards model, and a Mantel-Haenszel test. The ERG considers this unnecessary on the basis that heterogeneity is expected with respect to treatment arms across studies and it is only the relative treatment effect within studies, on some suitable scale, that is additive across studies. Furthermore, absence of evidence of heterogeneity with respect to treatment arms across studies would not be considered by the ERG sufficient justification to assume that the studies are estimating the same parameter of interest. However, the company concluded that the PanVd arms within PANORAMA-1[20] and PANORAMA-2[9] were estimating different parameters and excluded PANORAMA-1 from further consideration on the basis of the number and types of prior treatments received. An assessment of the effect of IsaPd versus PanVd on PFS was conducted using an MAIC of IsaPd from the ICARIA-MM study[4] and PanVd from the PANORAMA-2 study.[9] The comparison between treatments is in a population of patients defined by the PANORAMA-2 study rather than with respect to the target population (i.e. 4L). See Table 3 for details of the PANORAMA-2 study.

In Section K.4.4 of the CS, the company stated that "*OS data were not sufficiently mature for ICARIA-MM and not available for PANORAMA-1 (Table 40) [of the CS]. Furthermore, it was not possible to compare ORR as the trials used different response definitions (Table 41) [of the CS]. Therefore, these outcomes were not included in the MAIC.*"[3] In practice, all three outcomes were analysed.

The company applied the MAIC using individual patient data from ICARIA-MM and using aggregate data from PANORAMA-2. In the matching process the effective sample size for ICARIA-MM was reduced to 91. The MAIC was then used to obtain a HR for PanVd compared to IsaPd which was applied to the underlying survivor functions used for the IsaPd group used in the comparison of IsaPd and Pd.

3.4.1 Progression-free survival

The company included potential or known prognostic factors and/or treatment effect modifiers as covariates in its MAIC model in order to re-weight the PFS data from the ICARIA-MM[4] IsaPd arm to match the distribution of patient characteristics of the PanVd arm of the PANORAMA-2.[9] The following covariates were used: age (median); ECOG performance score; gender; the presence of one of Del17p, t(4;14) or t(14;16); International Staging System (ISS) stage at study entry; number of prior regimens (median); previous stem cell transplant; time since diagnosis (median); refractory to lenalidomide. It is not clear whether these represent all relevant prognostic factors and/or treatment effect modifiers.

The company fitted various parametric models to the weighted IsaPd and unweighted PanVd data separately to each treatment arm and with a covariate representing a treatment effect. The company assessed the proportional hazards assumption based on whether the two treatment arms on the log cumulative hazard plot versus log time are approximately parallel, whether the Schoenfeld residuals show a random pattern centred on zero, and whether a regression line fitted through the data has a non-statistically significant slope. The ERG believes that the appropriate basis for assessing whether hazards are proportional is to plot the log cumulative hazard against time not against log (time)[21] which is presented in Figure 19A, Appendix K.4 of the CS.[3] Section K.4.5.3.1 of the CS[3] states that "*the test of the linearity of the Schoenfeld residuals is not statistically significant, suggesting that the assumption of proportionality may be appropriate for this comparison.*" However, in the same section, the CS states that "*the test of the linearity of the Schoenfeld residuals is statistically significant, suggesting that a PH distribution (e.g. exponential, Weibull, Gompertz) may be inappropriate.*" The ERG is uncertain regarding which sentence is correct.

Not all models considered were proportional hazards models (e.g. the lognormal and log-logistic distributions are acceleration failure models), which further negates any discussion regarding proportional hazards. Figure 18B in Appendix K.4 of the CS[3] suggests that the hazard for IsaPd is relatively constant over at least the first 12 months, whereas the hazard for PanVd appears to increase over the first 12 months at least. Nevertheless, the ERG does not consider that an assessment of proportional hazards (or acceleration failure) is relevant in the context of an economic evaluation. At best this is a modelling assumption that is not necessary to make unless there is a clear clinical rationale for doing so; absence of evidence against a proportional hazards (or acceleration failure) assumption is not evidence to support a proportional hazards (or acceleration failure) assumption.

The company estimated that the HR from the Cox proportional hazards model for IsaPd compared with PanVd was 0.369 (95% CI 0.259 to 0.526) favouring IsaPd but stated that "*It should be noted that the test of the Schoenfeld residuals was statistically significant suggesting that the PH*

assumption may be invalid. As the HR for IsaPd vs PanVd was diminishing (benefits increasing) over time (see figure above), the estimated HR may be a reasonable estimate of the average HR during the period of observation but may underestimate the benefits of IsaPd in the long-term."

The ERG is concerned with the way the survival functions for each of IsaPd and PanVd were generated. The company generated the IsaPd survival function using a log normal (acceleration failure) model fitted to the 4L subgroup of the ICARIA-MM study and generated the PanVd survival function by imposing a HR from a Cox proportional hazards model of the MAIC-adjusted data. As Guyot *et al*.[22] wrote, "*from a statistical point of view, the Cox hazard ratio will not have the same numerical value as a hazard ratio that would be estimated by fitting the parametric model to both arms. Yet, if we believe that the parametric model correctly represents the standard treatment effect and we accept proportional hazards, then there is no reason to not use the parametric model to estimate the relative treatment effect. Second, overlaying the hazard ratio from one analysis onto a baseline arm from a different analysis will overstate the uncertainty in the analysis because the covariation between baseline and treatment effect that would be expressed in a single coherent analysis is lost*". Furthermore, while it may be reasonable to assume that the treatment effect is unaffected by the lines of treatment, the lognormal distribution is not a proportional hazards model and the combination of a hazard ratio and a lognormal model is inappropriate.

It is unclear to the ERG what is meant by restricted cubic spline Weibull, lognormal and log-logistic models. Weibull, lognormal and log-logistic models can be parameterised using a restricted cubic spline approach depending on the link function used and by including no additional knots. Figure 19B in Appendix K.4 of the CS[3] appears to recognise this but there is no formal discussion regarding the different model assumptions.

Figure 21 in Appendix K.4 presents Bayesian Information Criterion (BIC) statistics for the relative goodness-of-fit of each model to the observed data. However, the ERG is not confident with using these as the basis for model comparison in this submission. In particular, the ERG is concerned because the company states that "*The restricted generalised gamma is the best fitting distribution based on the Bayesian Information Criterion (BIC) statistic, however, this distribution failed to converge and should be disregarded*."[3] The issue is likely to be the way the treatment effect was defined in the three-parameter generalised gamma distribution and the scale on which the treatment effect was estimated.

The company stated that "*Separate HRs for TTD or PFS on treatment could not be computed because the PANORAMA-2 trial did not report KM curves for these outcomes and PFS is the closest proxy outcome available. HRs for PFS were therefore used for PFS, PFS on treatment, and TTD."*[3]

3.4.2 Overall survival

Despite stating in Section K.4.4 of the CS that OS data were not sufficiently mature, the company presented results of a MAIC for OS in Section K.4.5.3.2 of the CS.[3] As with PFS, the company estimated the baseline survival function for IsaPd with respect to the 4L subgroup of the ICARIA-MM study and estimated relative treatment effect using a Cox proportional hazards model of the MAIC adjusted data. The company considered a lognormal distribution (an acceleration failure model) to provide the best representation of the observed data while also concluding that it was reasonable to assume that the hazards for IsaPd and PanVd were proportional. Furthermore, there appears to be a typographical error as the company concluded that a Cox proportional hazards model showed that there was a statistically significant difference between treatments significant in favour of IsaPd despite the confidence interval for the HR crossing unity (HR= 0.642, 95% CI: 0.38, 1.082).

As before, the ERG is not confident that all of the models, for example the Generalised F distribution, are estimable from the sample data alone given the number of events in each treatment arm. Furthermore, it is unclear how the treatment effect is defined in some models (for example, the Generalised F distribution) or on what scale it is estimated.

As before, the company inappropriately projects a HR from a Cox proportional hazards model onto an acceleration failure model survival function (the lognormal) for IsaPd to generate the PanVd survival function. The magnitude of any inaccuracy associated with this is unknown, but it is unlikely to alter the conclusions of the company's economic analysis of IsaPd compared to PanVd.

Objective Response Rate (ORR)

In Section K.4.4 of the CS,[3] the company wrote that it did not consider a comparison of ORR on the basis that studies used different response definitions. Nevertheless, Section K.4.5.4 presents a MAIC between IsaPd and PanVd. No information is provided on the weights. Estimates of odds ratios and risk differences are provided according to unweighted and weighted data; these are virtually identical suggesting no adjustment for differences in study characteristics.

3.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

3.6 Conclusions of the clinical effectiveness section

3.6.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The clinical evidence relating to isatuximab with pomalidomide and dexamethasone for treating RRMM is based on the ICARIA-MM trial,[4, 11] a Phase III open-label RCT. The ERG is confident that no additional studies (published or unpublished) of isatuximab with pomalidomide and dexamethasone for treating RRMM are likely to have been missed.

3.6.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

The ERG is confident that the relevant population, intervention and comparators have been included in the CS. The primary outcome of the ICARIA-MM trial was PFS, assessed from the date of randomisation to the date of first documentation of progressive disease or the date of death from any cause, whichever came first, at the cut-off date (11th October 2018), which is a recommended outcome according to the EMA.[12] In the 4L population, the median PFS was greater in the IsaPd arm (13.31 months [95% CI: 7.425, not calculable]) than in the Pd arm (7.82 [95% CI: 4.468, 11.072]), and the stratified (by age) HR was 0.598 (95%: CI 0.348, 1.030), which the CS states represents a 40.2% risk reduction of disease progression or death in favour of IsaPd compared with Pd.[3] The EMA suggest that OS should demonstrate a trend towards superiority if PFS is used as a primary outcome.[12] Mortality events were reported in 21.2% and 39.7% of 4L patients in the IsaPd and Pd arms, respectively, with a median OS of 14.36 months (95%: CI 11.565, not calculable) in the Pd arm whilst the median OS had not been reached in the IsaPd arm (stratified HR 0.494 [95% CI 0.240, 1.015]), which indicates a trend for greater OS in the IsaPd arm. The OS data, however, were immature and final OS analyses are planned once 220 deaths have been observed. The effect of IsaPd on OS may have been impacted by an imbalance between the trial arms in the proportion of patients who received subsequent daratumumab. ORR and median TTP were higher in the IsaPd arm of the 4L population than the Pd arm. The median DOR was not calculable for both the IsaPd and Pd arms in the 4L population, and no clinically meaningful difference between treatment arms on EORTC QLQ-C30 scores and subscale scores, suggesting no QoL detriment of IsaPd in relation to treatment with Pd. In terms of AEs, IsaPd appears to be generally well tolerated.

3.6.3 Uncertainties surrounding the reliability of the clinical effectiveness

The first key uncertainty relates to the open-label nature of the trial, which may have introduced measurement bias, and may have altered patterns of oral medication use (e.g. for oral pomalidomide, the RDI of which was higher in the Pd arm than in the IsaPd arm). The impact of this element of study design is difficult to assess, however it is unlikely that this would have made no impact on the results.

The second key uncertainty relates to the post-hoc analysis and reporting of patients in the ICARIA-MM study at 4L of treatment. The 4L population is directly relevant to the proposed positioning of IsaPd within the treatment pathway, however the ERG has some reservations with this *post hoc* approach, as it was not a stratified group and does not have the protection of the randomisation when making comparisons between treatments.

A discrepancy between the arms in the use of subsequent daratumumab introduces uncertainty in the measurement of OS. Since subsequent daratumumab use (at 5L) is inconsistent with the current UK clinical management pathway for RRMM, this may compromise the generalisability of the ICARIA-MM study results to the UK context.

The ERG notes that the MAIC used to compare IsaPd and PanVd will have inherent uncertainties as detailed in Section 3.4. This also represents a key uncertainty.

4 COST EFFECTIVENESS

This chapter presents a summary and critique of the company's health economic analyses of isatuximab with pomalidomide and dexamethasone for the treatment of adult patients with RRMM. Section 4.1 presents a critique of the company's review of existing health economic analyses. Section 4.2 summarises the methods and results of the company's model. Sections 4.3 and 4.4 present the critique of the model and additional exploratory analyses undertaken by the ERG, respectively. Section 4.5 presents a discussion and critique of the available economic evidence.

The three key components of the economic evidence presented in the CS are: (i) a systematic review of the relevant literature, (ii) a report of the company's *de novo* economic evaluation and (iii) a presentation of the incremental cost effectiveness ratio (ICER) in terms of cost per quality-adjusted life year (QALY) gained. The company also provided an electronic version of their economic model developed in Microsoft Excel®. Following the clarification process the company submitted a revised version of the model that included updated estimates of the cost-effectiveness of IsaPd. For brevity, this report will only refer to the model (and results) received after clarification, unless explicitly stated otherwise. Despite advice provided by NICE, the company maintained the use of estimated confidential PAS discounts for daratumumab, pomalidomide and panobinostat in its base case, although results were also presented with these estimated discounts removed. The ERG has only reported on the results without inclusion of the estimated PAS discounts; results with the PAS discounts for pomalidomide, panobinostat and lenalidomide included are contained in a confidential report.

4.1 Company's review of published cost-effectiveness studies

4.1.1 Summary and critique of the company's search strategy

The company performed a three-in-one systematic literature search to identify: (i) economic evaluations of isatuximab and its comparators for treatment of patients with RRMM (CS Appendix H, pages 139-152); (ii) HRQoL studies for patients with RRMM (CS Appendices H and I, pages 185-198), and; (iii) resource used data for patients with RRMM in England (CS Appendices H, I and J, pages 212-224).[3]

The following sources were searched from inception until June 2019: MEDLINE and Epub Ahead of Print, In Process and & Other Non-Indexed Citations and Daily [via Ovid], Embase [via Ovid], Health Technology Assessment database [via CRD], NHS Economic Evaluation Database [via CRD], the Cost Effectiveness Analysis Registry [Center for the Evaluation of Value and Risk in Health], and the ScHARR Health Utilities Database [University of Sheffield]. Several cancer conference proceedings websites (American Society of Clinical Oncology, European Society for Medical Oncology, European

Haematology Association Congress, European Hematology Association, American Society of Hematology, European Society of Hematology) were searched covering the period from 2015 until 2019. The company carried out supplementary searches using the websites for several international HTA agencies (NICE, SMC, CADTH, ICER).

The company's searches are clearly and fully reported in Appendices H, I and J of the CS.[3] The ERG considers that they are comprehensive and would retrieve important citations relating to all eligible studies.

4.1.2 Summary of company's review findings

The company identified twenty studies that met the inclusion and exclusion criteria, of which 18 were cost-utility analyses. Four of these were company submissions to NICE: daratumumab monotherapy;[23] ixazomib with lenalidomide and dexamethasone;[24] panobinostat with bortezomib and dexamethasone[25]; and pomalidomide with low-dose dexamethasone,[26] which the company used to inform its submission. As none of the identified studies included isatuximab the company developed a *de novo* model for use in this appraisal.

4.2 Description of company's health economic analysis

4.2.1 Model scope

As part of its submission to NICE, the company submitted a fully executable health economic model programmed in Microsoft Excel®. A summary of the company's base case model is summarised in Table 5. The company's base case analysis assesses the incremental cost-effectiveness of IsaPd versus Pd in patients with relapsed or refractory multiple myeloma who have received 3 lines of prior therapies including lenalidomide and a proteasome inhibitor. Additional analyses were provided for patients who had received only two prior lines of treatment and for patients who had three or more lines of prior treatment.

Table 5: Summary of company's base case model

Population	Adults with relapsed or refractory multiple myeloma who have received 3 lines of prior therapies, including lenalidomide and a proteasome inhibitor (4th line of treatment)
Time horizon	15 years, assumed to represent a patient's lifetime
Intervention	Isatuximab (plus pomalidomide and dexamethasone) (IsaPd)
Comparator	Pomalidomide and dexamethasone (Pd)
Outcome	Incremental cost per QALY gained
Perspective	National Health Service (NHS) and Personal Social Services (PSS)
Discount rate	3.5% per annum for both health outcomes and costs
Price year	NHS Reference Costs (2017/2018); 2019 for drug costs

IsaPd - Isatuximab with pomalidomide and dexamethasone; NHS - National Health Service; Pd - Pomalidomide and dexamethasone; QALY - quality-adjusted life year; PSS - Personal Social Services

The company provide secondary cost-effectiveness analysis comparing IsaPd versus PanVd in Appendix K.4 of the CS,[3] "*in order to satisfy the requirements of the NICE scope*". The company claims that PanVd "*appears to be reserved for later line (i.e. ≥5th line) mainly due to its associated toxicities*". As stated in Section 2.3.3 this position was not universally supported by the clinicians providing advice to the ERG.

The economic analysis was undertaken from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) over a 15-year (lifetime) horizon. Cost-effectiveness is expressed in terms of the incremental cost per QALY gained. Unit costs are valued at 2017/2018 prices, although the drug costs use 2019 prices.[3, 27] Health outcomes and costs are discounted at a rate of 3.5% per annum.

Population

The modelled population relates to adult patients with RRMM, who have received 3 lines of prior therapies, including lenalidomide and a proteasome inhibitor (4th line of treatment). This population is consistent with a subgroup of the ICARIA-MM study,[11] the final NICE scope[6] and the anticipated marketing authorisation for isatuximab. At model entry, patients are assumed to have a mean age of 65.9 years, a body surface area (BSA) of 1.8m^2 of, and 51.8% of patients are assumed to be male.[3] The company states (CS, page 96) that *"although the patients entering the model are younger than those expected to be treated in the UK, evidence from ICARIA demonstrates consistent outcomes across all pre-specified subgroups including age (<75 years versus >=75 years) and number of previous lines (2 or 3 versus >3)".*[3] However, the ERG notes that similar relative outcomes, such as HRs, between subgroups does not necessarily translate into similar ICERs if there are differences in aspects such as underlying prognoses.

Clinical specialists consulted by the ERG agreed that the population of the study appears reasonably consistent with the population being treated in clinical practice in England, albeit with a smaller proportion of black patients than would be expected in the UK. Clinical advice stated that this racial discrepancy was unlikely to significantly affect applicability to patients with RRMM in the UK.

Intervention

The intervention evaluated in the submission is IsaPd. Within the model, isatuximab is assumed to be administered as an infusion at a dose of 10mg/kg on days 1, 8, 15, and 22 for the first four weeks; and on days 1 and 15 subsequently of four-week periods. Dexamethasone is assumed to be administered orally or as an IV at a dose of 20mg or 40mg on days 1, 8, 15 and 22 of every four weeks. Pomalidomide is assumed to be administered orally at a dose of 4mg on days 1 to 21 of every four weeks. The model also considers medication used prior to isatuximab infusion with the objective of

reducing the risk and severity of infusion reactions. Such interventions include: acetaminophen 650mg to 1000mg orally (paracetamol 1000mg); H2 antagonists (ranitidine 50mg IV); and cetirizine 50mg as an IV (as an equivalent to diphenhydramine 25mg to 50mg).[3]

Comparators

The comparator evaluated within the company's base case analysis is Pd, a combination of pomalidomide and dexamethasone, where the constituent parts are assumed to be administered according to the same schedule as the intervention. The model also includes the costs of acetylsalicylic acid, at a dose of 325mg given orally for 21 days of every four weeks.

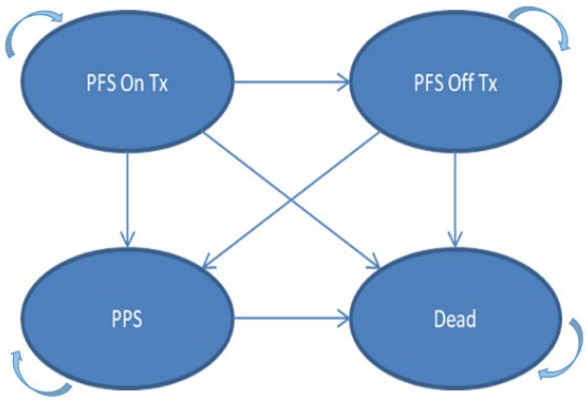
PanVd, the comparator presented in a secondary cost-effectiveness analysis (CS, Appendix K.3),[3] is a combination of panobinostat (20mg/day orally, for 6 days every three weeks); bortezomib (1.3mg/m^2 via injections, for 4 days in every three weeks for the first 24 weeks and then for 2 days every 3 weeks for 24 weeks); and dexamethasone (20mg/day orally, for 4 days every three weeks for the first 24 weeks and for 2 days every three weeks for 24 weeks). The dosing scheme for PanVd is based on the Summary of Product Characteristics (SmPC) for panobinostat from the EMA.[28]

Drug acquisition costs for IsaPd, Pd and PanVd over the patient's lifetime are based on the probability of patients remaining on each treatment based on time to treatment discontinuation (TTD) functions.

4.2.2 Model structure and logic

The general structure of the company's economic model is described in CS (pages 96-98),[3] as a partitioned survival model approach, based on four health states: (i) event-free on treatment; (ii) event-free off treatment; (iii) post-event, and (iv) death (see Figure 4). It is possible to remain in the same health state between cycles.

Figure 4: Company's model structure (adapted from CS, Figure 20)



The ERG notes that the original approach adopted by the company was chosen in preference to a more conventional three-state model in order to allow for the use of different utility values for patients conditional on whether people were on or off treatment. During the clarification process,[7] the company adopted an alternative approach to calculating the health state QALYs, where utility in the PFS and PD health states was assumed to be independent of whether or not the patient is on treatment. However, the structure that allows for different utilities to be included remains. As a result, the revised model can be considered to be operating as though it were a partitioned survival model with three health states: (i) progression-free and alive; (ii) post-progression and alive, and (iii) dead. For simplicity, the ERG reports parameters as though the model was constructed as a three-state partition survival model. No assumptions of patients being cured from the disease were explicitly introduced by the company in its submission and model. The ERG comments that the model was relatively cumbersome and had a file size approaching 40 Megabytes, which is excessive for a partitioned survival model.

Within the company's model, patients enter the model in the progression-free and alive state and receive 4L treatment with either IsaPd or Pd. PFS, TTD and OS are modelled using treatment group-specific parametric distributions fitted to time-to-event data for patients from the 4L subgroup in ICARIA-MM RCT.[11] A mortality constraint is applied to ensure that the probability of survival for the modelled population does not exceed that of the general population of the UK.[27]

The probability of being in each model state at time *t* is estimated for each health state as follows:

- PFS: This is calculated using the PFS survival function (constrained by the OS function and general population mortality) at time *t*.
- PPS: This is calculated as the difference between the cumulative survival probabilities at time *t* for OS and PFS;
- death: This uses the OS survival function (constrained by general population mortality) at time *t*.

Time on 4L treatment was estimated from TTD survival function.

HRQoL is assumed to be determined by the patient's health state (progression-free or post-progression) and the type of treatment received (IsaPd or Pd). Health utilities used in the model are based on the results of a generalised estimating equation (GEE) model fitted to derived EuroQoL Group self-report questionnaire with 5 dimensions (3 level) (EQ-5D-3L) data. EQ-5D-3L data were derived from the EQ-5D-5L data collected in ICARIA-MM, using the mapping algorithm reported by Van Hout *et al.*[29] EQ-5D-3L estimates were adjusted for patient-aging using the relationship reported by Ara and Brazier.[30] The company includes a QALY decrement to capture the decline in HRQoL

during the terminal phase of the disease, which was also derived from the trial data. The model does not explicitly include any QALY loss associated with Grade 3/4 AEs for IsaPd or Pd. The company states that the effects of AEs on HRQoL would already have been captured in the EQ-5D data collected from patients event-free and on treatment in ICARIA-MM (CS, page 129).[3]

The model includes costs associated with: (i) drug acquisition and administration; (ii) disease management ('follow-up and monitoring', and 'concomitant treatments'); (iii) treatments following disease relapse/progression; (iv) management of AEs; and (v) end of life care. Drug acquisition and administration costs are modelled using the TTD survival function, the planned treatment schedule, RDI and unit costs. Disease management costs include medical visits, blood tests and biochemistry, and the costs of concomitant treatments (granulocyte colony stimulating factor (GCSF), blood and platelet transfusions); these costs are presented in Section 4.2.4. Whilst the costs of the visits and tests are applied in all cycles to the number of patients in each health state, the costs of concomitant treatments are applied as once-only costs in the first model cycle to all patients. Costs related to the management of AEs are also applied as once-only costs in the first model cycle; end of life care costs are applied as a fixed cost in the cycle in which the patient died, while costs of treatments in 5L are added as a fixed sum in the cycle at which a patient discontinues.

The incremental health gains, costs and cost-effectiveness of IsaPd versus Pd are modelled in a pairwise fashion based on the difference in costs divided by the difference in QALYs for IsaPd and Pd, over a time horizon of 15 years using 1-week cycles. Half-cycle correction is not applied to account for the timing of events, due to the short cycle length. Secondary analyses are presented in the CS (Appendix K.3 and K.4)[3] for comparisons against IsaPd versus PanVd for 4L, and for IsaPd versus Pd for 3L, 3L+ and 4L+. This report focusses predominantly on the company's base case analysis, which is the comparison of IsaPd compared with Pd for patients with RRMM receiving 4L treatment.

4.2.3 Key assumptions employed in the company's model

The company's model employs the following key assumptions in its base case:

- PAS discounts for daratumumab, pomalidomide and panobinostat were applied despite prevailing NICE guidance; results without these discounts were also provided;
- An exponential distribution was used for modelling OS, and for TTD. A jointly-fitted lognormal model with a treatment effect covariate was used for PFS;
- Acquisition costs of the intervention and comparators (drug costs) are modelled using the TTD survival functions;
- HRQoL is assumed to be conditional on two factors: (i) whether a patient is in PFS or PPS (although in the revised model these were set to the same value), and (ii) which 4L treatment

was received, based on estimates derived from the GEE model fitted to the data collected in ICARIA-MM;

- A utility decrement of 0.225 (estimated from the GEE model) is applied for three months prior to death, irrespective of the treatment received, to reflect a deterioration on the quality of life in this period. The 12-week period was based on published literature and review of the study data;[11, 31, 32]
- The proportion of patients receiving 5L treatment following IsaPd or Pd were based on data from ICARIA-MM;[11] however, the mean duration of each therapy was based on external data;[33]
- The frequency of follow-up and monitoring interventions (physician visits, complete blood tests and biochemistry) were assumed independent of treatment and progression status, based on clinical opinion provided to the company;
- Only the top 10 most frequently prescribed medications were included in the costs of 5L treatment;
- The cost of terminal care was assumed to be the same irrespective of the treatment received (£894.15), based on a previous submission to NICE for pomalidomide;[34]
- The model considers only AEs that were reported in ≥5% of patients in any of the treatment arms of ICARIA-MM[11] and that were judged to be Grade 3 or higher in severity. The probabilities were taken from the observed data of 4L patients in ICARIA-MM[11] with the costs sourced from NHS Reference Costs 2017/18.[35] Disutilities were assumed to be already captured on the mean utility values generated from ICARIA-MM data.

The company's model employs the following additional key assumptions in its comparison of IsaPd and PanVd:

- The HRs obtained from the MAIC were applied to the survival functions for OS and PFS associated with IsaPd in the company base case; the HR obtained for PFS was assumed to be applicable to the survival function for TTD;
- The health state utilities and terminal decrement for patients on IsaPd were assumed to be applicable to PanVd;
- The probabilities of patients on PanVd having AEs, their duration, disutilities, and associated costs were estimated based on previous daratumumab NICE STA (TA510),[36] lenalidomide NICE STA,[37, 38] and other published sources.[39-45] The probabilities of having AEs were assumed to be applicable to patients on 4th line of treatment for RRMM, even if the original data were not specific to this group of patients.[3]
- The proportion of patients receiving each 5L therapy following IsaPd were assumed to be generalisable to PanVd.

4.2.4 Evidence used to inform the company's model parameters

The sources of evidence used to inform company's model parameters are summarised in Table 6. These are discussed in detail in the subsequent sections.

Table 6: Summary of evidence used to inform the company's base case analysis and comparison of IsaPd and PanVd

Parameter group	Source
Base case analysis – comparison of IsaPd and Pd for 4L	
Patient characteristics (age, BSA, weight, proportion of females)	The 4L subgroup in ICARIA-MM[4]
TTD – IsaPd and Pd	An exponential model fitted to observed TTD data for 4L subgroup in ICARIA-MM[11]
PFS – IsaPd and Pd	A jointly-fitted lognormal model with a treatment effect covariate fitted to observed PFS data from each treatment group (4L subgroup) in ICARIA-MM[11]
OS – IsaPd and Pd	An exponential model fitted to observed OS data from each treatment group (4L subgroup) in ICARIA-MM[11]
Mortality – general population constraint	Derived from interim life tables for England 2016-2018[27]
HRQoL for health states – IsaPd and Pd	GEE model fitted to EQ-5D-5L data collected from 4L subgroup on IsaPd or Pd in ICARIA-MM[11] (mapped to EQ-5D-3L using van Hout *et al*[11, 29])
End of life HRQoL decrement – IsaPd and Pd	GEE model fitted to EQ-5D-5L data collected from 4L subgroup on IsaPd or Pd in ICARIA-MM (mapped to EQ-5D-3L using van Hout *et al*)[11, 29]
Duration of the end of life HRQoL decrement	Based on previous literature and review of the data from ICARIA-MM[4, 31, 32]
HRQoL age-adjustment	Age- and gender-matched general population utilities based on published UK population norms from Ara and Brazier[30]
The proportion of patients experiencing AEs - IsaPd and Pd	Based on data from 4L subgroup on IsaPd or Pd in ICARIA-MM[11]
AE disutility – IsaPd and Pd	Not explicitly included. The company assumed that the utility values for PFS in ICARIA-MM[11] captured the effects of AEs on HRQoL.[3]
Drug acquisition costs – IsaPd and Pd	Unit costs from Electronic Market Information Tool (eMIT)[46] and British National Formulary (BNF),[47] estimates of BSA, weight and RDI obtained from ICARIA-MM[11]
Drug administration costs – IsaPd and Pd	Unit costs taken from NHS Reference Costs 2017/18[35]
Disease management costs (follow-up and monitoring) – IsaPd and Pd	Daratumumab NICE STA (TA510),[36] NHS Reference Costs 2017/18.[35] Clinical opinion was used for the frequency of monitoring.
Disease management costs (concurrent treatment) – IsaPd and Pd	Daratumumab NICE STA (TA510)[36] and pomalidomide submission to NICE (TA427);[34] unit costs taken from NHS Reference Costs 2017/18[35]
Post-progression treatment costs (subsequent therapy) – IsaPd and Pd	Unit costs from eMIT[46] and BNF[47]
Probability of receiving each of the subsequent therapy considered– IsaPd and Pd	Based on data for the ten most frequently received treatments in ICARIA-MM[11]
Mean duration of subsequent therapy – IsaPd and Pd	Values from external data.[33] PanVd submission to NICE,[48] and NHS regimen information sheets for etoposide and bendamustine.[49, 50]
Costs associated with AEs – IsaPd and Pd	AE frequencies based on ICARIA-MM;[11] unit costs taken from NHS Reference Costs 2017/18[35]
End of life care costs – IsaPd and Pd	Pomalidomide submission to NICE (TA427),[34] updated to 2017/2018 costs[35]
Additional analysis – evidence used to inform PanVd in the comparison of IsaPd and PanVd	

Parameter group	Source
for 4L	
OS – PanVd	An estimate of the HR for OS for PanVd vs. IsaPd from the MAIC-adjusted unanchored comparison between ICARIA-MM[11] (IsaPd) and PANORAMA-2[9] (PanVd), applied to the OS function for IsaPd
PFS – PanVd	An estimate of the HR for PFS for PanVd vs. IsaPd from the MAIC-adjusted unanchored comparison between ICARIA-MM[11] (IsaPd) and PANORAMA-2[9] (PanVd) was applied to the PFS function for IsaPd
TTD – PanVd	Estimates of the HR for PFS for PanVd vs. IsaPd from the MAIC-adjusted unanchored comparison were applied to the TTD function for IsaPd
HRQoL for health states – PanVd	The company assumed the same values as for IsaPd
End of life HRQoL decrement – PanVd	The company assumed the same values as for IsaPd and Pd
Probabilities of patients having AEs - PanVd	Estimates of the probabilities for PanVd are based on data from the daratumumab NICE STA (TA510);[36] values not specific to 4th line of treatment; which are adjusted by subtracting from it the probability of having each AE from the IsaPd treatment group (based on ICARIA-MM)[7, 11]
AE disutility – PanVd	AE estimates of the disutilities and their duration based on daratumumab NICE STA (TA510),[36] lenalidomide NICE STA,[37, 38] and other published sources[39-45]
Drug acquisition costs – PanVd	Unit costs from eMIT[46] and BNF;[47] regimen based on SmPC for panobinostat;[28] RDI based on PANORAMA-2 data[9]
Drug administration costs – PanVd	Unit costs taken from NHS Reference Costs 2017/18.[35]
Disease management costs (follow-up and monitoring) – PanVd	The frequency of physician visits and blood tests was assumed to be the same as for IsaPd and Pd
Disease management costs (concurrent treatment) – PanVd	The average number of interventions from daratumumab NICE STA (TA510);[36] unit costs taken from NHS Reference Costs 2017/18[35]
Post-progression treatment costs (subsequent therapy) – PanVd	Subsequent treatment after progression was assumed to be the same as for IsaPd and Pd
Probability of receiving each of the subsequent therapy considered – PanVd	The company assumed the same values as for IsaPd
Mean duration of subsequent therapy – PanVd	The company assumed the same values as for IsaPd and Pd
Costs associated with AEs – PanVd	Estimated costs for each AE from Daratumumab NICE STA (TA510)[36] and NHS Reference Costs 2017/18.[35]
End of life care costs – PanVd	The company assumed the same costs per patient as for IsaPd and Pd

AE - adverse event; BSA - body surface area; PFS - progression-free survival; EQ-5D - EuroQoL 5-dimensions; GEE - generalised estimating equation; HRQoL - health-related quality of life; IsaPd – isatuximab in combination with pomalidomide and dexamethasone; eMIT - Electronic Market Information Tool; OS - overall survival; PanVd – panobinostat, with bortezomib and dexamethasone; Pd – pomalidomide and dexamethasone; RDI - relative dose intensity; STA – single technology appraisal; TA – technology appraisal.

4.2.4.1 *Patient characteristics at model entry*

The model assumes that patients enter the model aged 65.9 years and approximately 51.8% of the modelled cohort is assumed to be male. Patients are assumed to have a mean body surface area (BSA)

of 1.8m^2 and to weigh 73.14kg. These characteristics reflect the population of patients who have received three prior lines of treatment (4L) in the ICARIA-MM trial.[11]

4.2.4.2 *Description and critique of the company's survival analyses*

For each of the outcomes used in the economic model (PFS, OS and TTD), six standard parametric models were fitted (exponential, Weibull, log-logistic, lognormal, generalised gamma and generalised F distributions). Survival functions were also estimated using restricted cubic splines (RCS).

The company's preferred base case model was based on the treatment effect diagnostics and test of linearity of Schoenfeld residuals for the proportional hazards assumption, statistical goodness-of-fit, visual comparison with empirical Kapan-Meier survival functions and the clinical plausibility of the projected survival functions.

The company fitted the same models to each arm of the ICARIA-MM study,[4] partly to allow estimation of a single treatment effect. However, this approach assumes that the treatment effect is constant over time on some appropriate scale (i.e. proportional hazards, acceleration failure or proportional odds). While this approach is a convenient modelling assumption for estimating a treatment effect, there is no stated clinical reason why the treatment effect should be constant over time. Making this assumption when the treatment effect is not constant will generate biased estimates of population mean survival. To relax this assumption, the company also fitted separate but identical models to each treatment arm.

Section B.3.3 of the CS[3] states that "*the RCS distributions have six parameters, not including the knots*". However, a proportional hazards restricted cubic spline model with a single covariate representing a constant treatment effect and including a single knot is:

$$\ln[H(t; z_1)] = \gamma_0 + \gamma_{10} x + \gamma_{20} v_1(x) + \beta_1 z_1$$

Thus, a proportional hazards model including one knot has four parameters, while a non-proportional hazards model including a single knot would have six parameters. Hence, it is not clear to what parameters the company is referring.

The results of the MAIC may appear to lack face validity as PanVd is estimated to have a shorter time to progression than Pd, [PanVd HR compared with IsaPd (0.369 (0.259 – 0.526)) whereas Pd compared with IsaPd (0.598 (0.348 – 1.030))] but is estimated to have a shorter survival [PanVd HR compared with IsaPd (0.642 (0.380 – 1.082)) whereas Pd compared with IsaPd (0.494 (0.240 – 1.015))]. Typically, PFS is correlated with OS as death is counted as an event in both metrics.

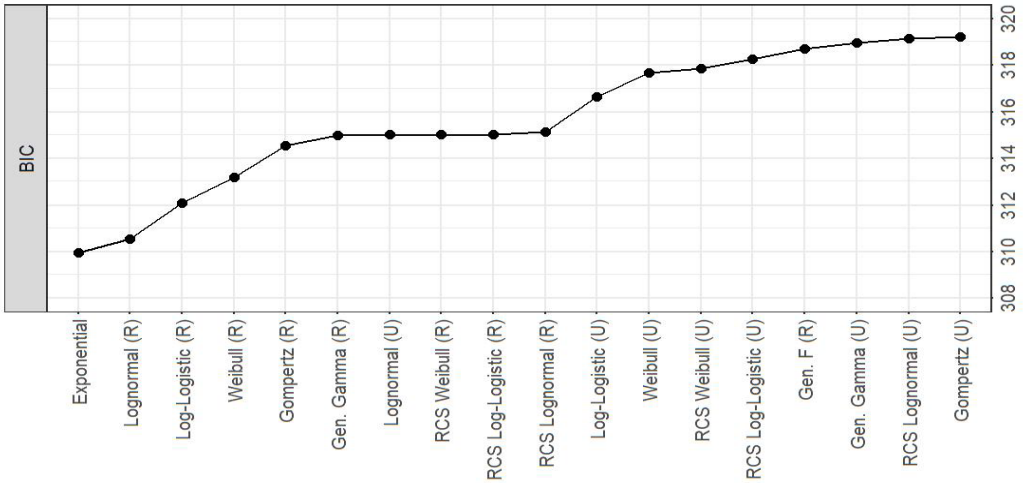
4.2.4.2.1 Description and critique of the company's model fitting to OS data

Section B.3.3 of the CS refers to restricted cubic spline Weibull, lognormal and log-logistic models. However, it is not clear to the ERG what is meant by this. Weibull, lognormal and log-logistic models can be parameterised using a restricted cubic spline approach depending on the link function used and by including no additional knots. These analyses should give the same results as for standard parameterisations of these models.

The company assesses the clinical plausibility of projected survival functions against available external evidence (e.g. the MM-003 study[51]) and through a series of interviews with three NHS consultant haematologists. The ERG notes that assessing the consistency of extrapolations against data from other studies is difficult without taking into account differences in patient characteristics. Furthermore, the ERG believes that asking clinical experts to indicate which, in their opinion, is the most plausible of a set of survival functions is unlikely to be very informative for the following reasons: first, it implies that a clinical expert is able to express their opinion about the true proportion of patients surviving at each time without any uncertainty; second it ignores uncertainty associated with the parameters of each model, and the consequent uncertainty associated with the survival functions; and third survival functions derived from distributions with very different underlying hazards may look similar to clinical experts. In practice, questions regarding beliefs about the proportion of patients event-free at different follow up times should be asked using a formal elicitation of experts' beliefs before seeing data from a study, although the ERG acknowledges that this was unlikely to be possible in this case. However, based on the information presented in the CS, the ERG considers an exponential distribution, as selected by the company, to provide a reasonable representation of the OS data. The BIC data for the fits to OS provided within the CS are reproduced in Figure 5. The company used (R) to denote jointly-fitted models with a treatment effect covariate models and (U) models fitted independently to each arm.

The ERG notes that other functions (jointly-fitted lognormal, jointly-fitted log-logistic and jointly-fitted Weibull models in particular) provide similar a fit to the known OS data, but these were not independently explored within the scenario analyses undertaken in the CS, despite the fact that two of three NHS consultant haematologists preferred the extrapolation from the Weibull model.[3] The company justified the decision to not use the Weibull survival function as "*almost all patients are dead by 5 years on Pd arm and by 10 years on IsaPd. There are no patients alive after 10 years, which is inconsistent with the feedback and published evidence regarding long term survival for a small proportion of patients with RRMM*". The company states that, by contrast, the exponential survival function predicts approximately 10% alive at 10 years, and almost no patients alive at 15 years. Clinical advice to the ERG suggests that there would be practically no patients alive at 10 years given present treatment options.

Figure 5: Bayesian Information Criteria fit to OS data for the 4L population of ICARIA-MM (reproduced from Figure 22 of the CS)



The plot of the six best-fitting parametric models to the OS KM data are shown in Figures 27 and 28 of the CS.[3] However as they are not shown on a single graph the ERG has provided the fits to the IsaPd OS KM data in Figure 6 and the fits to the Pd OS KM in Figure 7. The models used in the company base case are shown in Figure 8.

Figure 6: Selected model fits to the KM OS data for IsaPd

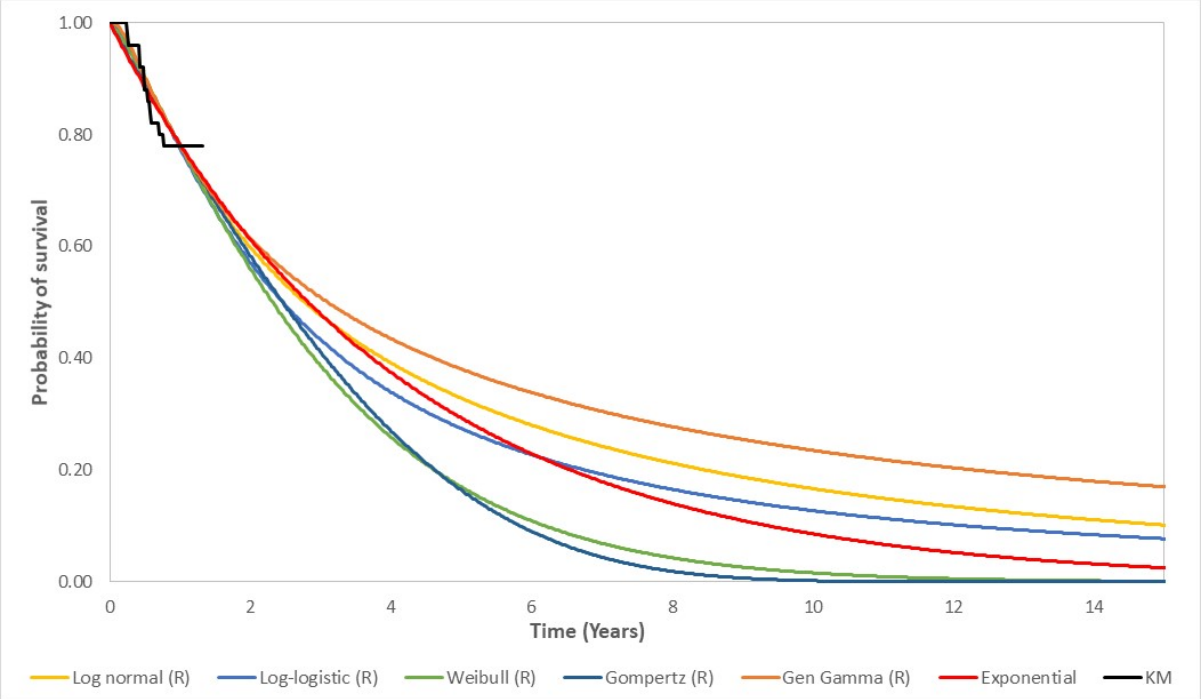


Figure 7: Selected model fits to the KM OS data for Pd

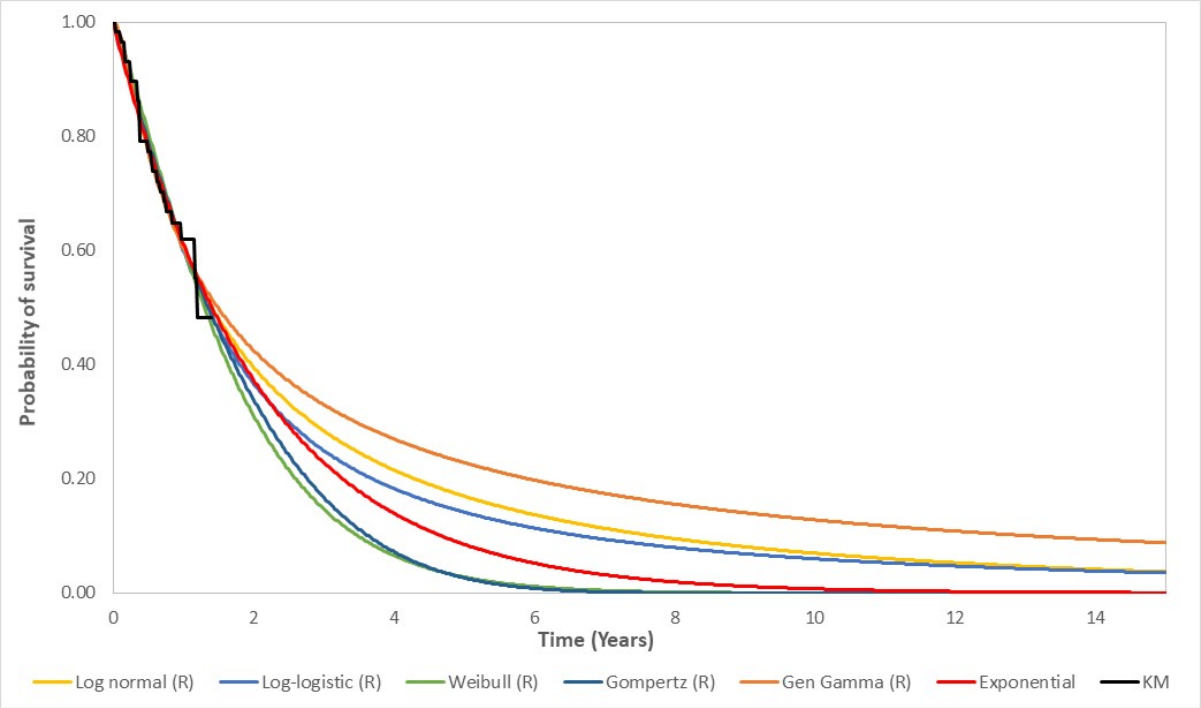
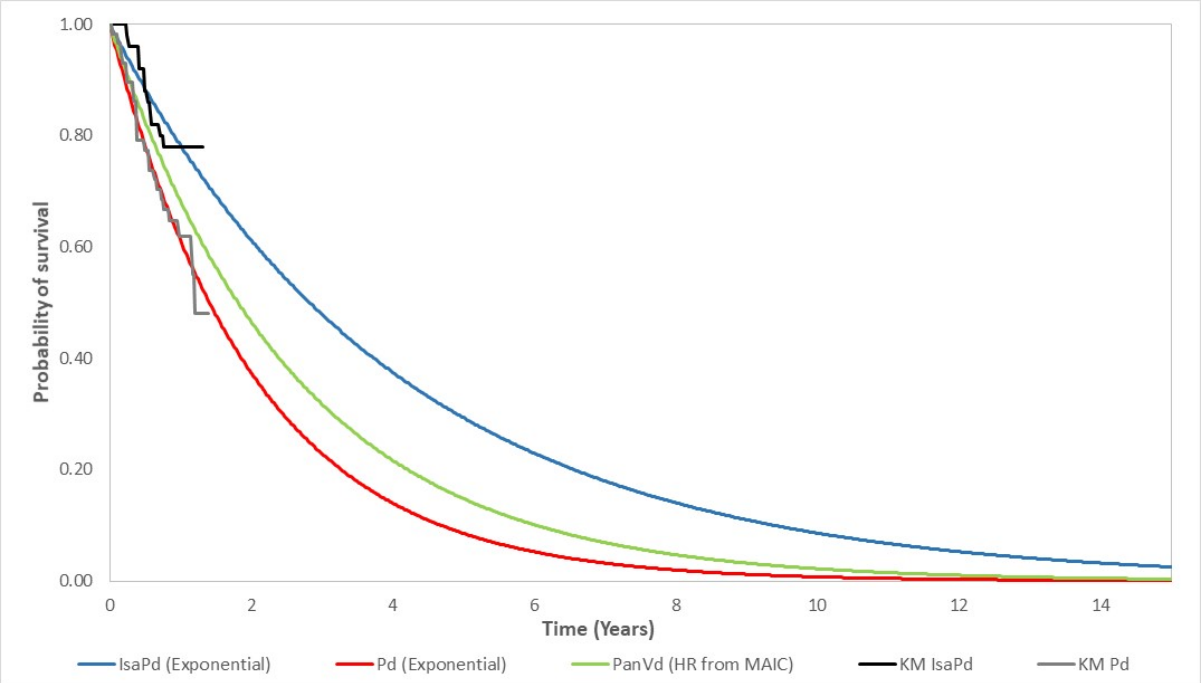


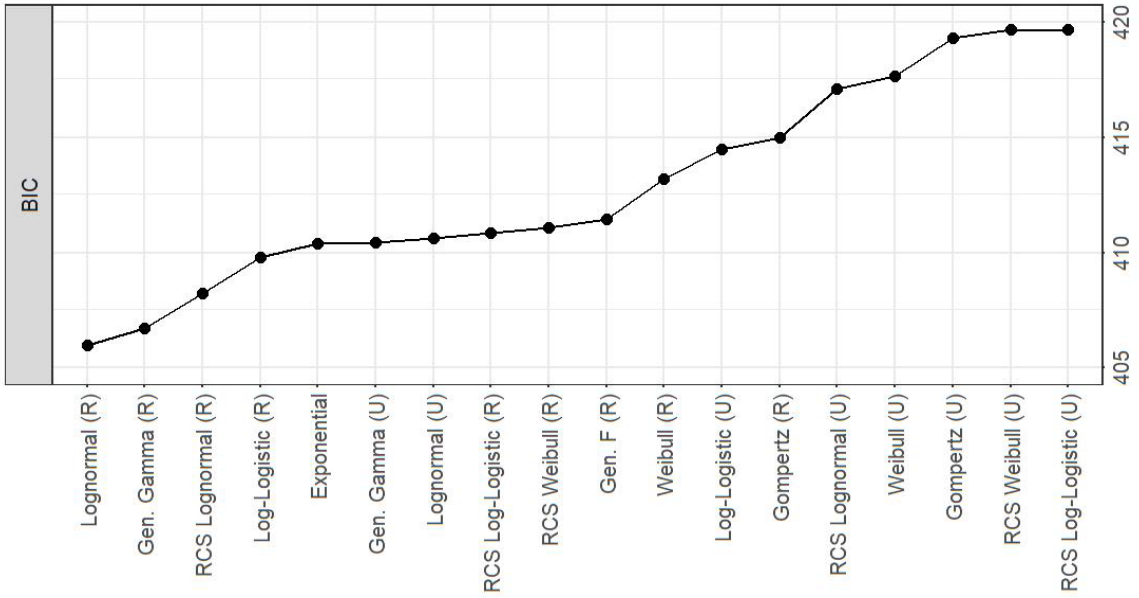
Figure 8: The models used for OS in the company's base case



4.2.4.2.2 Description and critique of the company's model fitting to PFS data

The BIC data for the fits to PFS provided within the CS[3] are reproduced in Figure 9. The ERG notes that there is a difference of approximately 5 in BIC with respect to the jointly-fitted lognormal distributions and independently fitted lognormal distributions.

Figure 9: Bayesian Information Criteria fit to PFS data for the 4L population of ICARIA-MM (reproduced from Figure 26 of the CS)



Whilst the ERG typically prefers independently-fitted models, as each treatment arm should represent the data better, it is noted that the difference in BIC reflects the fact that separate models are penalised more than a model allowing for an acceleration factor because of the use of an additional parameter. The ERG considers the jointly-fitted lognormal model with a treatment effect covariate to provide a reasonable representation of the PFS data. Alternative models for the PFS data that were preferred by clinical experts (the RCS jointly-fitted Weibull, the jointly-fitted Weibull, the exponential and the jointly-fitted Gompertz) were considered by the company in sensitivity analyses. The plot of the six best-fitting parametric models to the PFS KM data are shown in Figures 31 and 32 of the CS.[3] However, as these are not on a single graph the ERG has provided the fits to the IsaPd PFS KM data in Figure 10 and the fits to the Pd PFS KM in Figure 11. The models used in the company base case are shown in Figure 12.

Figure 10: Selected model fits to the KM PFS data for IsaPd

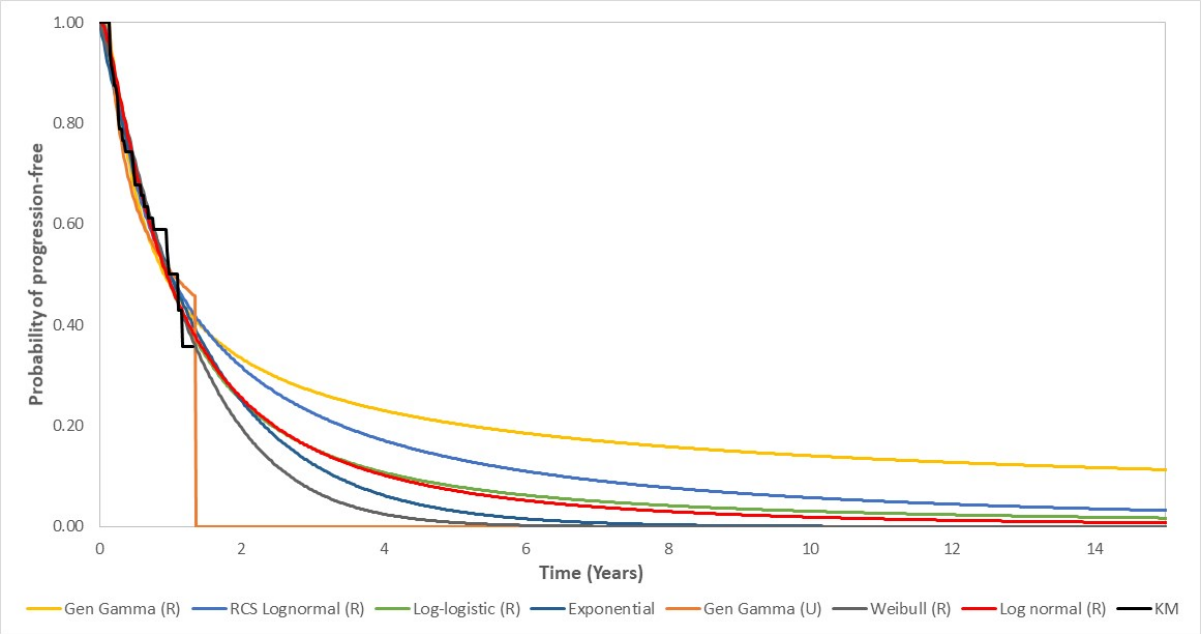


Figure 11: Selected model fits to the KM PFS data for Pd

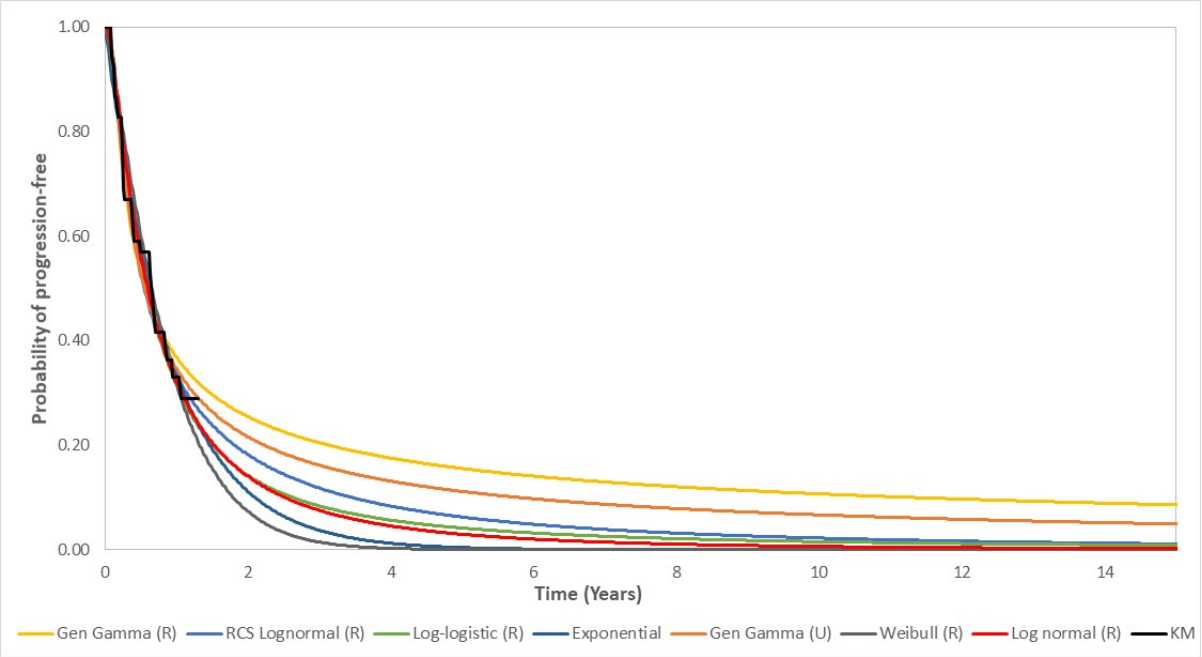
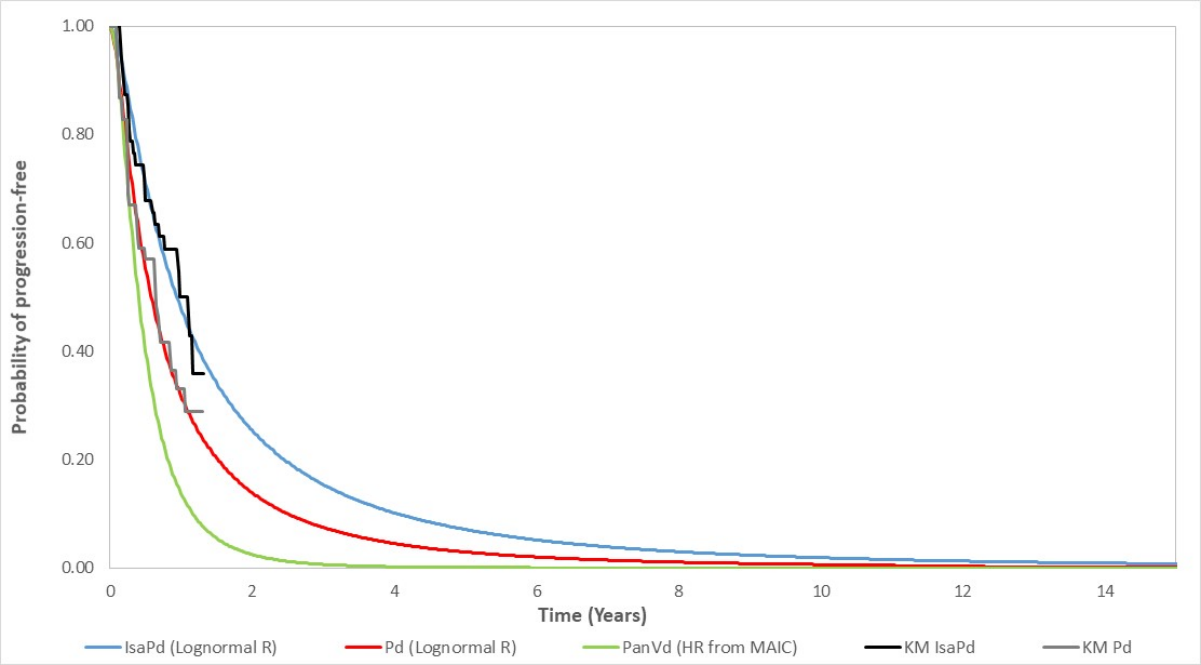


Figure 12: The models used for PFS in the company's base case



4.2.4.2.3 Description and critique of the company's model fitting to TTD data

The BIC data for the fits to TTD provided within the CS[3] are reproduced in Figure 13. It is seen that the exponential model has the lowest BIC value, which is nearly 5 lower than the remaining models. The plot of the six best-fitting parametric models to the TTD KM data are shown in Figures 35 and 36 of the CS.[3] However, as these are not on a single graph the ERG has provided the fits to the IsaPd TTD KM data in Figure 14 and the fits to the Pd TTD KM data in Figure 15. The models used in the company base case are shown in Figure 16.

The ERG believes that the exponential distribution, as selected by the company, appears to provide a good fit to the data but notes that the company did not report the results of scenario analyses using alternative functions.

Figure 13: Bayesian Information Criteria fit to TTD data for the 4L population of ICARIA-MM (reproduced from Figure 34 of the CS)

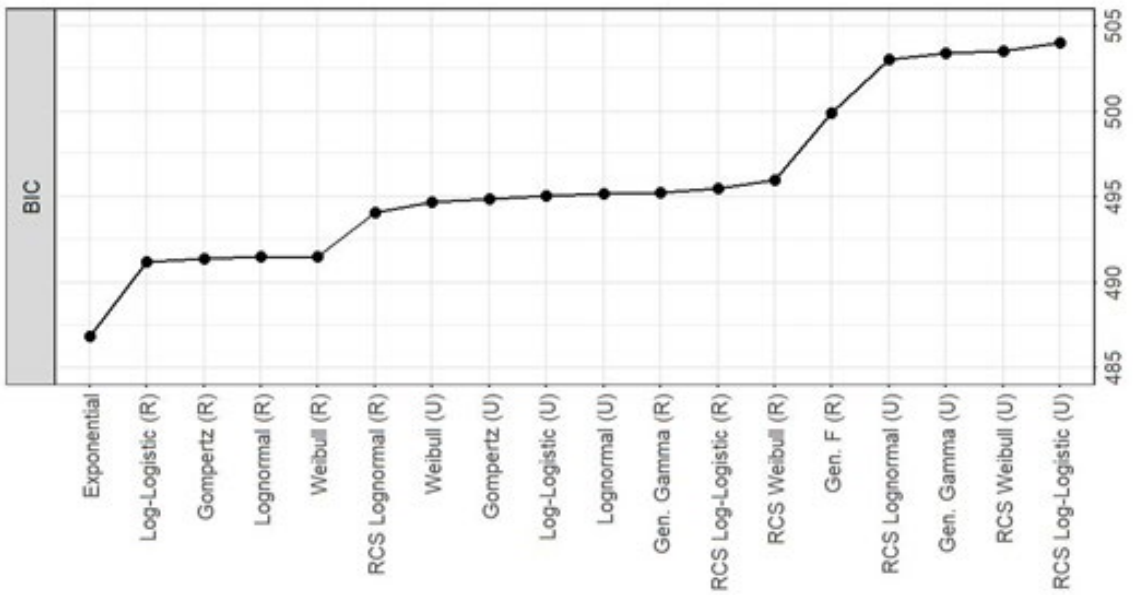


Figure 14: Selected model fits to the TTD PFS data for IsaPd (redacted – commercial in confidence)

[redacted]

Figure 15: Selected model fits to the TTD PFS data for Pd (redacted – commercial in confidence)

Figure 16: The models used for TTD in the company's base case (redacted – commercial in confidence)

Summary plots for the chosen fit to OS, PFS, PFS on treatment and TTD were provided in Figures 37 to 40 of the CS. The ERG is cautious regarding whether these plots are correct, as in the clarification process (question B6)[7] it was acknowledged that Figure 37 was incorrect and the ERG identified later that the projections of TTD using an exponential function appear different between Figures 35 and 39,

with the ERG suspecting Figure 39 is erroneous. During the fact check process the company confirmed that Figures 37 to 40 of the CS were incorrect.

The ERG comments that when estimating parameters in time-to-event models using frequentist methods, the analysis generates a variance-covariance matrix. Although these estimates are approximations, they can be used to sample parameter estimates in time-to-event models from an approximate multivariate normal distribution.

4.2.4.3 HRQoL

Health state utility values

HRQoL data used in the company's model is based on data collected in ICARIA-MM[11] using the EQ-5D-5L questionnaire. Within the trial, the questionnaire was administered at day 1 of the first treatment course, and all subsequent cycles and at the 30-day end of treatment (EOT) visit and during the post-treatment follow-up period (60±5 days after last treatment administration).[11]

The company fitted a GEE model to the available data, using baseline utility value, treatment group, health state, and proximity to death as covariates whilst accounting for repeated measures in the same patient. Utility values were estimated for PFS and PPS health states, and also included a terminal decrement associated with the deterioration in the health of patients in the period ahead of death. The company has mapped the EQ-5D-5L data to the EQ-5D-3L using the algorithm reported by Van Hout *et al.*[29] and UK tariffs were applied to the 3L scores.[52]

The characteristics of the utility data and the estimates applied in the company's model are summarised in Table 7.[7] Utilities for the event-free state are assumed to be dependent on treatment group, whilst utilities for the post-progression state are assumed to be independent of previous treatment. These utilities values used in the model are applied in all cycles of the model.

Table 7: Mapped EQ-5D-3L estimates used in company's model (adapted from the company's model)

Health state	Mean utility†	
	IsaPd	Pd
Progression-free	0.719	0.717
Post-progression	0.611	0.611
End-of life (terminal) decrement	0.225	0.225

† Underlying utility values for PanVd were assumed equal to IsaPd. However, 0.035 QALYs were deducted in the first cycle to account for differing AE profiles.

The model applies age-adjustment to the health state utilities based on UK general population norms reported by Ara and Brazier.[30] Utilities for patients being treated with PanVd are assumed to be the same as for IsaPd patients.[7]

QALY losses due to AEs

A summary of the estimates for QALY losses related to AEs applied in the company's model is displayed in Table 8. The model does not include any decrements in QALYs associated with Grade 3 or higher AEs for IsaPd or Pd. The company states that the effects of AEs on HRQoL would already have been captured in the EQ-5D data collected from patients event-free and on treatment in ICARIA-MM (CS, page 129).[3] In response to clarification question B10 which asked whether it was possible that administering the EQ-5D prior to the dose of isatuximab would potentially overestimate utility, the company responded that "*it is typical to collect this data at the start of treatment cycle. In ICARIA-MM trial, EQ-5D were administered on day 1 of each cycle (i.e. every 2 weeks) therefore it is reasonable to assume that serious adverse reactions are likely to be captured in the subsequent EQ-5D questionnaire completed by the patient.*" The ERG believes that this is reasonable.

For patients in the PanVd group, the frequency of each AE considered was obtained from data for PanVd in the PANORAMA-2 study (reported in the company submission to NICE for daratumumab).[36] The company notes, however, that these values were not specific to patients who had 3 prior lines of treatment (CS, Appendix K.4, page 321).[3] The company calculates the difference between the IsaPd rates and those for PanVd to estimate the net change in utility from AEs.

Table 8: Frequency, associated utility decrements, mean duration and total disutilities associated with Grade ≥3 AEs (adapted from the company's model)

Adverse event	Frequency of AEs			Utility decrements	Mean duration (days)ǂ	Total disutilities		
	IsaPd	Pd	PanVd*			IsaPd§	Pd§	PanVd
Abdominal distension	0.0%	0.0%	7.3%	0.05	28	0.0	0.0	0.004
Abdominal pain	0.0%	0.0%	5.5%	0.05	28	0.0	0.0	0.004
Acute kidney injury	3.9%	5.2%	-3.9%	0.37	28	0.0	0.0	0.028
Anaemia	0.0%	1.7%	15.0%	0.31	180	0.0	0.0	0.153
Asthenia	2.0%	3.4%	7.0%	0.12	28	0.0	0.0	0.009
Dehydration	0.0%	0.0%	5.5%	0.00	28	0.0	0.0	0.000
Diarrhoea	3.9%	0.0%	16.1%	0.10	28	0.0	0.0	0.008
Fatigue	5.9%	0.0%	14.1%	0.12	28	0.0	0.0	0.009
Febrile neutropenia	13.7%	5.2%	-13.7%	0.39	28	0.0	0.0	0.030
Flatulence	0.0%	0.0%	5.5%	0.00	28	0.0	0.0	0.000
Hypercalcaemia	2.0%	5.2%	-2.0%	0.08	28	0.0	0.0	0.006
Hypokalaemia	2.0%	0.0%	5.3%	0.20	0.02	0.0	0.0	0.000
Hypophosphatemia	0.0%	0.0%	6.0%	0.07	28	0.0	0.0	0.005
Hypotension	0.0%	1.7%	9.1%	0.07	0.01	0.0	0.0	0.000
Nausea	0.0%	0.0%	5.5%	0.10	28	0.0	0.0	0.008
Neutropenia	43.1%	29.3%	-28.1%	0.15	28	0.0	0.0	0.011
Pneumonia	17.6%	15.5%	-2.6%	0.19	7	0.0	0.0	0.004
Sepsis	0.0%	0.0%	9.1%	0.20	28	0.0	0.0	0.015
Septic shock	0.0%	3.4%	5.5%	0.20	28	0.0	0.0	0.015
Syncope	0.0%	0.0%	9.1%	0.1	28	0.0	0.0	0.008
Thrombocytopenia	5.9%	10.3%	58.1%	0.31	28	0.0	0.0	0.024
Total	**-**	**-**	**-**	**-**	**-**	**0.0**	**0.0**	**0.035**

IsaPd – isatuximab in combination with pomalidomide and dexamethasone; Pd – pomalidomide and dexamethasone; PanVd – panobinostat, with bortezomib and dexamethasone

*Notes: * the rates for PanVd include the adjustments made by the company "reflecting the difference in the incidence of AEs for PanVd versus IsaPd" (clarification response, page 54).*[7]

ǂ - In the company's model, the average duration of each AE was converted to years.

§ - In the company's base case, AE-related QALY decrements for IsaPd and Pd are assumed to be zero.

4.2.4.4 Resource costs

The model includes costs associated with: (i) drug acquisition and administration; (ii) disease management; (iii) treatments following disease relapse/progression; (iv) management of AEs, and (v) end of life care. These costs are summarised in Table 9.

Table 9: Summary of costs applied in the company's model

Cost parameter	Base case analysis		Additional analysis
	IsaPd §	Pd	PanVd
Drug costs (per week, first cycles*)	[redacted]	[redacted]	[redacted]
Administration costs (per week, first cycles*)	[redacted]	[redacted]	[redacted]
Drug costs (per week, subsequent cycles*)	[redacted]	[redacted]	[redacted]
Administration costs (per week, subsequent cycles*)	[redacted]	[redacted]	[redacted]
Disease management – event-free (per week)	£38.73	£38.73	£38.73
Disease management – progressed disease (per week)	£38.73	£38.73	£38.73
Disease management – other costs (once-only)	£679.08	£660.01	£313.16
Subsequent treatment drug and administration costs (post-progression, once-only, applied to discontinuers in each cycle)	[redacted]	[redacted]	[redacted]
End of life care (once-only)	£894.15	£894.15	£894.15
Grade 3+ AEs (once-only)	£1,618.37	£1,156.19	£1,948.84

AE - adverse event; IsaPd – isatuximab in combination with pomalidomide and dexamethasone; PanVd - panobinostat, with bortezomib and dexamethasone; Pd – pomalidomide and dexamethasone.
*Notes: * For the first 4 weeks for IsaPd and 8 weeks for PanVd.*
§Includes PAS for isatuximab.

(i) Drug acquisition and administration costs

Drug acquisition and administration costs are modelled as a function of the mean body weight or BSA observed in ICARIA-MM,[11] the planned treatment schedule, relative dose intensity (RDI) and unit costs (Table 10). Treatment schedules involve a reduction in the number of days the drug is administered after the first 4 weeks of treatment, in the case of isatuximab in IsaPd. Based on its list price, the cost per pack of 100mg vial of isatuximab (1 days' supply) is [redacted]. The company has an agreed PAS which takes the form of a simple price discount of [redacted]; the discounted cost per pack of IsaPd is therefore [redacted]. In secondary analyses, the company has provided results that do not include confidential PAS discounts for other drugs, which is consistent with NICE guidance. Drug prices were taken from the electronic Market Information Tool (eMIT) and the British National Formulary (BNF).[46, 47]

The company has used the distribution of patients using 20mg/40mg and oral/IV dexamethasone in each treatment arm in ICARIA-MM to estimate the costs of dexamethasone as part of the IsaPd intervention and the Pd comparator. The costs of IsaPd also included premedication drugs, which included 1000mg of paracetamol, 50mg of ranitidine and 50mg of cetirizine being administered on the

same days as isatuximab. The costs of Pd included the costs of acetylsalicylic acid for 21 days on the same days as pomalidomide.

Administration costs for each treatment are calculated assuming that only the highest cost of each treatment component would be applied in each cycle, and were based on NHS Reference Costs 2017/2018 (codes SB11Z to SB15Z).[35] Estimates for each treatment period for drug and administration costs are applied to patients on treatment in each cycle, obtained from the chosen TTD function estimated from data in ICARIA-MM.[11] The ERG notes that this is likely to introduce some inaccuracy as it will not take into consideration the exact timings of drug administration and treatment discontinuation.

The drug acquisition costs for PanVd were based on the SmPC for panobinostat;[28] and data from the PANORAMA-2 trial;[9] there is a dose reduction, for bortezomib and dexamethasone after the first 24 weeks of treatment and a maximum period of treatment of 48 weeks. The drug and administration costs for PanVd are calculated based on the TTD function for IsaPd, to which a fixed HR of [redacted], based on the unanchored MAIC is applied.

Table 10: Dosing, treatment schedules and drug cost per cycle for first-line treatments included in the company's model

Regimen	Regiment component	Administration route	Dosing schedule	RDI	Drug costs per week	NHS reference code	Administration costs per week
IsaPd	Isatuximab	IV	10mg/kg, 4 days/first 4 weeks; 10mg/kg, 2 days/subsequent periods of 4 weeks	[redacted]	[redacted]§	SB13Z (first dose); SB15Z (subsequent doses)	[redacted]
	Pomalidomide	Oral	4mg/day, 21 days/every 4 weeks	[redacted]	£2,221.00	SB11Z (first dose) *; none (subsequent doses)	£32.90(w1-4) */ £0 (w5+)
	Dexamethasone	Oral or IV	20 or 40mg/day, 4 days/ every 4 weeks	[redacted]	£15.41 (weighted)	None(first dose), SB15Z (subsequent IV doses), none (subsequent oral doses)*ǂ	£0.00*ǂ
	Premedication (Paracetamol, Ranitidine and Cetirizine)	IV	Paracetamol 1000mg, ranitidine 50mg and cetirizine 50mg on the same days as isatuximab	[redacted]	£0.58 (w1-4)/ £0.29 (w5+)	None(first dose), SB15Z (subsequent IV doses)*ǂ	£0.00*ǂ
Pd	Pomalidomide	Oral	4mg/day, 21 days/every 4 weeks	[redacted]	£2.221.00	SB11Z (first dose) *; none (subsequent doses)	£32.90(w1-4) */ £0 (w5+)
	Dexamethasone	Oral or IV	20 or 40mg/day, 4 days/every 4 weeks	[redacted]	£20.00 (weighted)	None(first dose), SB15Z (IV) (subsequent IV doses) †ǂ	£233.23ǂ
	Acetylsalicylic acid	Oral	325mg/day, 21 days/every 4 weeks	[redacted]	£0.10	SB11Z (first dose) *; none (subsequent doses)	£32.90(w1-4) */ £0 (w5+)
PanVd	Panobinostat	Oral	20mg/day, 6 days/every 3 weeks	72.9%	£1,552.00	none	£0.00
	Bortezomib	Injection	1.3mg/m^2, 4 days/every 3 weeks for the first 24 weeks; then 2 days/every 3 weeks for the subsequent 24 weeks	79.8%	£1,016.51 (w1-24)/ £508.25 (w25+)	SB12Z (first and subsequent doses)	£232.54 (w1-24)/ £116.27 (w25+)
	Dexamethasone	Oral	20mg/day, 4 days/every 3 weeks for the first 24 weeks; then 2 days/every 3 weeks for the subsequent 24 weeks	87.5%	£53.33(w1-24)/ £26.67	SB11Z (first dose) *; none (subsequent doses)	£43.87(w1-3) */ £0.0 (w4+)

*§Includes PAS for isatuximab. *The company uses only the highest value of administration costs for each treatment arm; therefore, the value is not actually used.† The administration costs of dexamethasone taking orally were costed as being £0.00 in all cycles.ǂ The ERG believes that there is an error in this calculation; please see Section 4.3.2 for more details.*

(ii) Disease management costs

Disease management costs are related to resource use for follow-up, monitoring and concomitant treatments available to patients throughout their disease, such as medical visits, blood tests and biochemistry, GCSF, red blood and platelet transfusions.

The costs within the model related to follow-up and monitoring (physician visits, complete blood count tests and biochemistry) use the assumed cost per cycle which is applied to the state occupancy for PFS and PPS. Unit costs for each of these interventions were based on the NICE technology appraisal for daratumumab (TA510),[36] updated by the company to 2017/2018 values, with the frequencies of visits based on clinical opinion and assumed to happen every month indefinitely independent of health state or treatment group.

The costs of concomitant treatments (GCSF, blood and platelet transfusions) are applied as once-only costs to all patients. The number of procedures received per patient and the rates of patients receiving each intervention for IsaPd and Pd patients are based on data from ICARIA-MM,[7, 11] whilst these values for patients receiving PanVd were based on NICE technology appraisals for daratumumab (TA510) and pomalidomide (TA427).[36, 53] Unit costs of these procedures were based on NHS Reference Costs 2017/2018.[35] Disease management costs used within the model for IsaPd, Pd and PanVd are summarised in Table 11.

The ERG notes some discrepancies between the revised values reported by the company for the rates of patients receiving GCSF, blood and platelet transfusions and the number of these procedures received per patient in the clarification response (clarification response B19, Table 20)[7] and the updated submitted model. Additionally, the ERG notes that these rates for patients receiving PanVd have changed between the original submission and the clarification with no reason provided. It is not clear which data were intended to be used by the company. The ERG has assumed that the values within the model are correct and has explored the impact of the alternative values on the ICER. As this impact was relatively small, less than £110 per QALY gained compared to Pd, and less than £500 per QALY gained compared to PanVd, the ERG used the values within the model and did not pursue this issue further. During the fact check process the company stated that "*Rates of patients receiving GCSF, blood and platelet transfusions and the numbers of these procedures received per patient for those receiving IsaPd and Pd were edited during the clarification process as recommended by the ERG. The values used are highlighted in clarification response B26. To allow for incorporation of different numbers of administrations by treatment, the model had been amended during the clarification process.*"

Table 11: Summary of health state resource use and costs (adapted from the company's updated model)

Resource	Rates for receiving concomitant treatments			Average interventions per patient (whole time horizon)			Frequency – all states (weekly)	Unit cost	Costs applied in the model*		
	IsaPd	Pd	PanVd	IsaPd	Pd	PanVd			IsaPd	Pd	PanVd
Physician visit	-	-	-	-	-	-	0.23014	£164.80	£37.90	£37.90	£37.90
Complete blood count test	-	-	-	-	-	-	0.23014	£2.51	£0.58	£0.58	£0.58
Biochemistry	-	-	-	-	-	-	0.23014	£1.11	£0.26	£0.26	£0.26
GCSF	10.3%	13.8%	20.0%	2.3	2.4	1	-	£52.70	£12.54	£17.45	£10.54
RBC transfusion	19.0%	41.4%	20.0%	1.8	2.8	3	-	£132.72	£45.31	£153.77	£79.63
Platelet transfusion	62.1%	50.0%	20.0%	4.3	4.2	4.79	-	£232.76	£621.23	£488.80	£222.98

EFS - event-free survival; IsaPd – isatuximab in combination with pomalidomide and dexamethasone; PanVd - panobinostat, with bortezomib and dexamethasone; Pd – pomalidomide and dexamethasone.

*Note: *Expressed as weekly costs for physician visits, complete blood count test and biochemistry and as once-only costs for GCSF, RBC and platelet transfusions.*

(iii) Costs of subsequent treatments (following disease relapse/progression)

The model includes the costs associated with treatments for relapse/progression after 4L treatment. Subsequent treatment included the ten treatments most frequently received by patients after progression in ICARIA-MM; the rates of patients receiving each treatment differ by treatment group, and are based on utilisation data for IsaPd and Pd patients from this study.[11] The company has assumed the same proportions for IsaPd would apply to PanVd patients in its secondary analyses.

The costs of post-relapse/progression treatment include drug acquisition and administration, which are based on unit costs from BNF, eMIT, NHS Reference Costs 2017/2018 and the average duration of treatment estimated from external data (Kantar Health Study of treatments in RRMM in Western Europe, NHS regimen information sheets, and a company's submission for PanVd (TA380)).[25, 33, 35, 46, 47, 49, 50, 54] These costs are summarised in Table 12, and are applied as a single cost to patients who discontinued treatment with IsaPd, Pd or PanVd in each cycle, irrespective of whether they have relapsed/progressed or died.

The ERG also notes that the company's clarification response states that according to clinical opinion, "*there were some differences in the post study treatments in ICARIA-MM vs UK clinical practice*" (clarification response, question B13).[7] However, the company states that "*These differences have been tested in the SA [sensitivity analyses]. The resultant ICER was £128,798 (with only PAS discount on isatuximab, a slight increase over the base case)*".

The ERG noted that thee was inconsistency in the proportion of people receiving daratumumab at 5L reported in the CS and used in the model. This was a potential concern as it appeared that the model may have used data for subsequent therapies from a later cut point than other outcomes such as OS. The ERG notified NICE of this on the 7th January 2020 but had not received a response from the company at the time of writing. The ERG has assumed that the values in the model are correct and comments that it is unlikely that the use of alternative figures would reduce the company's base case below £50,000 per QALY. As such, this has not been mentioned further within this report.

Table 12: Estimated costs of subsequent treatments (adapted from the CS, Tables 55 and 56, and the updated model)

Treatment	Rates for receipt subsequent treatments (IsaPd and PanVd)	Rates for receipt subsequent treatments (Pd)	Cost per pack	Drug Costs	Admin Costs	Total drug and administration costs (Isa and PanVd) *	Total drug and administration costs (Pd)*
Bendamustine	10.71%	11.90%	£75.13	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib	25.00%	16.67%	£762.38	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib	17.86%	21.43%	£1,056.00	[redacted]	[redacted]	[redacted]	[redacted]
Daratumumab	7.14%	38.10%	£1,440.00	[redacted]	[redacted]	[redacted]	[redacted]
Etoposide	10.71%	0.00%	£11.50	[redacted]	[redacted]	[redacted]	[redacted]
Thalidomide	3.57%	0.00%	£298.48	[redacted]	[redacted]	[redacted]	[redacted]
Lenalidomide	14.29%	2.38%	£4,368.00	[redacted]	[redacted]	[redacted]	[redacted]
Melphalan	10.71%	0.00%	£45.38	[redacted]	[redacted]	[redacted]	[redacted]
Panobinostat	3.57%	0.00%	£4,656.00	[redacted]	[redacted]	[redacted]	[redacted]
Pomalidomide	7.14%	7.14%	£8,884.00	[redacted]	[redacted]	[redacted]	[redacted]
Total	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]

IsaPd – isatuximab in combination with pomalidomide and dexamethasone; PanVd - panobinostat, with bortezomib and dexamethasone; Pd – pomalidomide and dexamethasone.
** Total costs after the application of the proportions of patients receiving each subsequent treatment.*

(iv) AE management costs

Costs related to the management of AEs are applied as once-only costs in the first model cycle, to all patients in each treatment group. Unit costs were estimated using NHS Reference Costs 2017/2018.[35] The frequency of events for IsaPd and Pd were obtained from data for 4L patients in the ICARIA-MM trial,[11] whilst the probabilities of having any of the AEs for PanVd were obtained from the company's submission to NICE for daratumumab's appraisal by NICE.[36] The frequencies, unit costs and estimates of costs due to AEs are presented in Table 13. The ERG notes that the mean duration of each AE, used in the estimates of AE-related utility decrements, was not directly accounted for when calculating these costs. Further, the unit costs used within the model did not match those reported within the CS (Table 54); the ERG was unsure of the reason for this discrepancy but believes that the choice of unit cost would not affect the ICER significantly.

Table 13: Frequency, unit costs and total costs associated with Grade ≥3 AEs (adapted from CS, Table 39, Appendix K.4, Table 57 and company's model)

Adverse event	Frequency of AEs			Unit costs	Total costs		
	IsaPd	Pd	PanVd		IsaPd	Pd	PanVd
Abdominal distension	0.0%	0.0%	7.3%	£2,490.55	£0.00	£0.00	£181.81
Abdominal pain	0.0%	0.0%	5.5%	£2,490.55	£0.00	£0.00	£136.98
Acute kidney injury	3.9%	5.2%	0.0%	£3,279.81	£128.62	£169.65	£0.00
Anaemia	0.0%	1.7%	15.0%	£575.01	£0.00	£9.91	£86.25
Asthenia	2.0%	3.4%	9.0%	£727.55	£14.27	£25.09	£65.48
Dehydration	0.0%	0.0%	5.5%	£0.00	£0.00	£0.00	£0.00
Diarrhoea	3.9%	0.0%	20.0%	£525.41	£20.60	£0.00	£105.08
Fatigue	5.9%	0.0%	20.0%	£727.55	£42.80	£0.00	£145.51
Febrile neutropenia	13.7%	5.2%	0.0%	£6,697.31	£919.24	£346.41	£0.00
Flatulence	0.0%	0.0%	5.5%	£0.00	£0.00	£0.00	£0.00
Hypercalcaemia	2.0%	5.2%	0.0%	£2,566.41	£50.32	£132.75	£0.00
Hypokalaemia	2.0%	0.0%	7.3%	£471.57	£9.25	£0.00	£34.28
Hypophosphatemia	0.0%	0.0%	6.0%	£471.57	£0.00	£0.00	£28.29
Hypotension	0.0%	1.7%	9.1%	£693.34	£0.00	£11.95	£63.02
Nausea	0.0%	0.0%	5.5%	£727.55	£0.00	£0.00	£39.68
Neutropenia	43.1%	29.3%	15.0%	£693.34	£299.09	£203.22	£104.00
Pneumonia	17.6%	15.5%	15.0%	£531.10	£93.72	£82.41	£79.67
Sepsis	0.0%	0.0%	9.1%	£3,005.41	£0.00	£0.00	£273.19
Septic shock	0.0%	3.4%	5.5%	£3,005.41	£0.00	£103.63	£165.30
Syncope	0.0%	0.0%	9.1%	£0.00	£0.00	£0.00	£0.00
Thrombocytopenia	5.9%	10.3%	64.0%	£687.95	£40.47	£71.17	£440.29
Total	**-**	**-**	**-**	**-**	**£1,618.37**	**£1,156.19**	**£1,948.84**

IsaPd – isatuximab in combination with pomalidomide and dexamethasone; Pd – pomalidomide and dexamethasone; PanVd – panobinostat, with bortezomib and dexamethasone

Notes: ǂ *- In the company's model, the average duration of each AE was converted to years.*

(v) End of life care costs

Costs related to terminal care were based on the NICE technology appraisal for pomalidomide (TA427),[53] and are also applied as once-only costs in the first model cycle to patients who died in any

cycle. The unit cost used by the company (£894.15) was derived from a scenario analysis which considered the distribution of patients who received care during the last week prior to death in a hospital setting, hospice, or used home services, and updated to 2017/2018 values.[3]

4.2.5 Model evaluation methods

The CS[3] base case presents incremental cost-effectiveness ratios (ICERs) for IsaPd versus Pd as a comparator. Results are presented using the deterministic and probabilistic versions of the model. The probabilistic ICERs are based on 1,000 Monte Carlo simulations. The ERG notes that the distributions used in the probabilistic sensitivity analysis (PSA) are not presented in the CS. Scrutiny of the model indicated that in generating sampled values the company used one of the following: modified 95% confidence intervals; bootstrapped data from the ICARIA-MM trial, or assumed that standard errors were assumed to be 25% of the mean, logged where appropriate. The ERG has identified limitations in the method used to generate sampled values for the health state utilities; these are discussed in further detail in Section 4.3.2. The results of the PSA are presented as a cost-effectiveness plane and as cost-effectiveness acceptability curves (CEACs) for IsaPd versus Pd.

Deterministic sensitivity analyses (DSAs) are presented for IsaPd versus Pd using tornado plots. Some of these analyses involve varying parameters according to their 95% CIs where available, or using +/- 25% of the expected value where 95% CIs were not available.

During the clarification process, pairwise ICERs and PSA results (cost-effectiveness planes and CEACs) were reported by the company for IsaPd versus PanVd for patients at 4L. DSAs using tornado plots for this comparison, results for IsaPd versus Pd using the ITT population in ICARIA-MM[11] (3L+) patients who received only 2 prior lines of treatment (3L) and patients with 3 or more prior lines of treatment (4L+) were not reported by the company using the updated model.[7] The ERG could produce these using the company's revised model but has not included these for brevity.

4.2.6 Company's model validation and verification

The CS (pages 169-170)[3] describes the company's model validation activities, which involved checking for errors, using different computers, comparing results of DSA and PSA against priors and point estimates, and testing the model on extreme values ("*pressure testing*"). The company states that an additional validation was conducted by an external agency, but no details were provided about which activities it involved, nor was supporting evidence presented regarding the outputs of these activities in terms of external validity.

4.2.7 Company's model results

The probabilistic and deterministic results presented in this section are based on the updated version of the company's model submitted in response to the clarification process; Table 14 presents the central estimates of cost-effectiveness generated using the company's model for the comparison of IsaPd versus Pd. For readability, the ERG has termed the results without an estimate of the PAS for drugs other than isatuximab as the company's base case. This is line with NICE guidance.

The probabilistic version of the updated model suggests that IsaPd is expected to generate an additional 1.63 LYs and 1.06 QALYs per patient compared to pomalidomide with dexamethasone; the corresponding ICER is £130,321 per QALY gained. The deterministic version of the model produces a lower ICER of £118,816 per QALY gained.

Table 14: Company's base case results - IsaPd versus Pd (based on the company's updated model and clarification response, discounted values)

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
Probabilistic model							
IsaPd	[redacted]	[redacted]	[redacted]	1.628	1.055	£137,519	**£130,321**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic model							
IsaPd	[redacted]	[redacted]	[redacted]	1.649	1.071	£127,267	**£118,816**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year IsaPd – isatuximab in combination with pomalidomide and dexamethasone; Pd – pomalidomide and dexamethasone; PanVd – panobinostat, with bortezomib and dexamethasone

The company presented the CEACs for IsaPd versus Pd in its clarification response (question B2, Page 31).[7] Assuming willingness-to-pay (WTP) thresholds of £30,000, and £50,000 per QALY gained, the company's model suggests that the probability that IsaPd generates more net benefit than Pd is 0.2%, and 1.6% respectively.

The company has not presented revised results for the deterministic univariate sensitivity analyses following the clarification process. However, the ERG comments that the ICER was only below £100,000 per QALY gained on two occasions, one when the RDI for pomalidomide in the Pd arm was increased by 50% and one where the RDI for isatuximab was reduced by 25%. The ERG notes that different assumptions used to model time-to-event data were not considered in this analysis.

Company's scenario analyses

In the initial submission, the company had undertaken several scenario analyses for IsaPd versus the Pd comparator, which are presented from pages 166 to 168 of the CS.[3] Although the results of these

analyses were not presented in the clarification response, they are present in the updated model provided by the company.[7]

The scenarios involved: not considering medication wastage in the model; using EQ-5D-5L utility values instead of 3L utilities; changing the proportion of patients receiving subsequent therapy and its mean duration based on expert opinion or previous HTA submissions; using expert opinion to estimate the mean duration of AEs; using survivor functions for modelling TTD, PFS and OS that would favour or disfavour IsaPd; assuming treatment discontinuation upon progression (using jointly-fitted lognormal or exponential distributions); using data from a previous STA[36] for some of the disease management costs; changing discount rates for outcomes and costs to 1.5%; assuming time horizons of 5, 10 and 20 years, and; using the weight distribution from the trial for dosage of isatuximab treatment. The company also presented extreme scenarios called 'favourable inputs' and 'unfavourable inputs', where all these modifications in the inputs, with the exception of the use of EQ-5D-5L utility values, were combined in order to result in the most favourable and unfavourable ICER for IsaPd.

Generally, most of the analyses produced ICERs that were similar to the company's base case scenario. However, scenarios that use distributions that would favour IsaPd (using a Weibull survival function fitted independently to each arm for TTD, and jointly-fitted RCS Weibull functions for PFS and OS) and consider no medication wastage, result in ICERs below £100,000 per QALY gained (£73,070 and £97,551 per QALY gained, respectively). In contrast, the scenarios that use unfavourable distributions for IsaPd (using a jointly-fitted log-logistic for TTD, jointly-fitted RCS lognormal for PFS and jointly-fitted lognormal for OS), assuming treatment discontinuation upon progression (using restricted lognormal distributions) and changing the time horizon length to 5 years, lead to ICERs above £150,000 per QALY gained (£196,696, £167,452 and £195,911 per QALY gained, respectively). The company also explored an alternative scenario using distributions based on expert clinical feedback (using jointly-fitted Weibull distributions for PFS and OS and maintaining the exponential distribution for TTD). This scenario results in an ICER for IsaPd versus Pd of £170,026 per QALY gained. The scenario that explores the most favourable combination of inputs for IsaPd results in the lowest ICER of these analysis (£55,158 per QALY gained), whilst the most unfavourable combination of inputs for IsaPd results in an ICER of £207,327 per QALY gained.

Company's additional analyses

The company has presented deterministic and probabilistic revised results for the pairwise comparison of IsaPd versus PanVd in its clarification response;[7] these are summarised in Table 15. IsaPd produces more LYGs and QALYs than Pd, at a lower cost. The ICER for IsaPd versus PanVd is higher than the base case analysis, estimated at £248,197 per QALY gained for the probabilistic analysis.

Table 15: Company's additional analysis results - IsaPd versus PanVd (based on the company's updated model and clarification response, discounted values)

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
Probabilistic model							
IsaPd	[redacted]	[redacted]	[redacted]	1.056	0.791	£196,393	**£248,197**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic model							
IsaPd	[redacted]	[redacted]	[redacted]	1.144	0.849	£184,053	**£216,856**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year
IsaPd – isatuximab in combination with pomalidomide and dexamethasone; PanVd – panobinostat, with bortezomib and dexamethasone

The company has not presented revised results for the deterministic univariate sensitivity analyses following the clarification process. However, the ERG comments that the ICER for IsaPd versus PanVd is greater than £150,000 per QALY gained regardless any changes in the parameters investigated by the company. The ERG notes that different assumptions used to model time-to-event data were not considered in these analyses.

The scenario analyses for IsaPd versus the PanVd comparator produced similar results to those for the main analysis, whereby the use distributions that would favour IsaPd (using Weibull functions fitted independently to each arm for TTD, and jointly-fitted RCS Weibull functions for PFS and OS) results in ICERs of £153,572 per QALY gained, whilst changing the time horizon length to 5 years lead to an ICERs of £363,241 per QALY gained. The scenarios that explore the most '*favourable*' and '*unfavourable*' combinations of inputs for IsaPd compared with PanVd results in ICERs of £140,966 and £283,187 per QALY gained, respectively. The simultaneous use of clinician-selected survivor functions for OS (jointly-fitted Weibull) and PFS (jointly-fitted Weibull) results in an ICER for IsaPd versus PanVd of £310,241 per QALY gained.

4.3 Critical appraisal of the company's health economic analysis

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying health economic model upon which this was based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.

- Double-programming of the deterministic version of the company's model to fully assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any apparent errors in the implementation of the model.
- Examination of the correspondence between the description of the model reported in the CS[3] and the company's executable model.
- Re-running the PSA, DSAs and scenario analyses presented within the CS[3] and clarification response.[7]
- Where possible, checking of key parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

4.3.1 Adherence to the NICE Reference Case

The company's economic analysis is generally in line with the NICE Reference Case[55] (see Table 16). Each element is discussed in further detail within the ERG report.

Table 16: Adherence of the company's economic analyses to the NICE Reference Case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The company's health economic analysis is generally in line with the final NICE scope;[6] except that the population within the company's base case is narrower than specified within the scope (restricted to those at 4L). The company has provided supplementary analyses for 3L and 4L+ to comply with the scope. As noted in Section 2.3.2, the company has not yet been granted an EU marketing authorisation for IsaPd in this indication.
Comparator(s)	As listed in the scope developed by NICE	The NICE scope[6] specifies two comparators: Pd and PanVd. The company's base case focusses on Pd as the comparator; nevertheless, the company undertook an exploratory analysis of IsaPd compared with PanVd "*in order to meet the requirements of the scope*".
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Direct health effects for patients were used. Health impacts on caregivers were not included in the analysis.
Perspective on costs	NHS and PSS	The analysis adopts an NHS and PSS perspective. However, scrutiny of the model indicates that no PSS costs have been included in the company's model.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The results of the analyses are presented in terms of the incremental cost per QALY gained for IsaPd versus Pd (and IsaPd versus PanVd in additional analysis). The company has also chosen to present results in terms of cost per LYG.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 15-year time horizon. Approximately 97.5% of patients have died in the IsaPd group and 100% in the Pd group by the end of the modelled time horizon (and 99.7% in the PanVd group).
Synthesis of evidence on health effects	Based on systematic review	Time-to-event outcomes (TTD, PFS and OS), HRQoL estimates and AE frequencies for patients receiving IsaPd and Pd are based on data from a subgroup of patients (4L) from ICARIA-MM study;[11] this was the key study included in the company's systematic review of clinical evidence. Health outcomes for patients who receive PanVd are based on the results of a MAIC and assumptions. HRQoL losses due to AEs for PanVd compared to IsaPd are based on published literature.

Element	Reference case	ERG comments
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health gains are valued in terms of QALYs. The ICARIA-MM RCT[4] recorded EQ-5D-5L values which were mapped to EQ-5D-3L values.[29]. A GEE regression model was fitted to the EQ-5D-3L data.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	HRQoL gains were directly reported by patients.
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	The company applied the UK EQ-5D tariff to the derived EQ-5D-3L data.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains.
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	Resource costs include those relevant to the NHS. Unit costs were valued at 2017/18 prices with drug costs set at 2019 prices.

AE - adverse event; CS - company's submission; EFS - event-free survival; ERG - Evidence Review Group; EQ-5D - EuroQoL 5-dimensions; HRQoL - health-related quality of life; ITT - intention-to-treat; OS - overall survival; PSS - Personal Social Services; QALY - quality-adjusted life year

4.3.2 Main issues identified within the critical appraisal

In general, the ERG believed the revised model structure and the parameter values used were appropriate for the decision problem. However, some limitations were identified. Box 1 summarises the main issues identified within the ERG's critical appraisal of the company's economic analyses. These issues are discussed in further detail in the subsequent sections.

Box 1: Main issues identified within the critical appraisal undertaken by the ERG

(1)	Identification of model errors
(2)	The time horizon is too short to capture all of the gains associated with IsaPd treatment
(3)	Lack of reporting of sensitivity analyses relating to the functions used to model time-to-event data
(4)	Potentially inaccurate estimation of drug acquisition and administration costs
(5)	That drugs assumed to be used in 5L would not be used in England
(6)	Potential face validity violations in the utilities sampled within the PSA
(7)	Underestimation of uncertainty
(8)	Uncertainty in the clinical evidence

(1) Identification of model errors

Incorrect formulae applied in relation to QALY losses at the end of life

Within the company's model, the QALY decrement associated with reduced HRQoL at the end of life is applied incorrectly as the negative value is subtracted rather than added to overall QALYs. This error would slightly decrease the ICERs of IsaPd compared with Pd and PanVd when amended.

Incorrect application of administration costs associated with dexamethasone

Within the model, the company weighted the costs of dexamethasone to take into consideration the proportion of patients receiving this drug intravenously and those receiving it orally. However, this was not taken into account when calculating the average administration costs. Incorporating the weighting reduces the costs associated with Pd, but has no impact on the costs of IsaPd as only the highest administration cost was assumed. Accordingly, the ICER for IsaPd compared with Pd increases.

(2) The time horizon is too short to capture all of the gains associated with IsaPd treatment

The company's base case uses a time horizon of 15 years at which point 2.5% of modelled patients in the IsaPd group are alive, 0.3% in the PanVd group and 0.1% in the Pd. The additional QALYs accrued by these patients would not be included in the company's base case and the ICERs for IsaPd compared with Pd and PanVd would decrease.

(3) Lack of reporting of sensitivity analyses relating to the functions used to model time-to-event data

Whilst the model has the functionality to use different survival distributions to model time-to-event data (TTD, PFS and OS), the reporting of the impact of the use of alternatives on the ICER is lacking. The ERG would have preferred to see the results reported using a more extensive range of alternative time-to-event models.

(4) Potentially inaccurate estimation of drug acquisition and administration costs

The time cycle within the company's model (one-week) is shorter than the frequency at which treatments are provided, for example, isatuximab which is given fortnightly after the first four weeks. Within its model the company calculated an average weekly cost rather than explicitly incorporating isatuximab costs every fortnight, as such, drug costs are artificially reduced by people discontinuing in the week that a treatment is provided, as the second weekly costs would not be used. The ERG believes that amending this assumption would increase the ICERs of IsaPd compared with Pd and PanVd.

(5) Drugs assumed to be used in 5L that would not be used in England

Within the ICARIA-MM RCT,[4] patients who progressed received treatments that are not recommended in England, for example, daratumumab, or that clinical advice to the ERG suggested would be rarely used, for example, lenalidomide. The ERG does not know how the ICERs of IsaPd compared with Pd and PanVd would change were the costs and benefits of such treatments removed.

(6) Potential face validity violations in the utilities sampled within the PSA

Within the PSA it was possible that the sampled mean utility for patients in progressed disease could be higher than that for patients in PFS; the ERG does not believe this to be plausible. The ERG believes that amending this limitation is unlikely to affect the central estimate of the ICERs of IsaPd compared with Pd and PanVd.

(7) Underestimation of uncertainty in the decision problem

The ERG notes that it is likely that the uncertainty within the decision problem has been underestimated. Factors contributing to this include: (1) several AEs that are included in the model without allowing for parameter uncertainty; (2) several parameter values are set at zero, which implies that it is known that the AEs do not occur in the population of patients treated with the particular treatment in question; (3) whilst the model includes AEs for which Grade 3 or higher events were reported in at least 5% of the patients in any of the treatment arms of ICARIA-MM or for the relevant pivotal trials of the key comparators it is not clear what impact rare but important adverse events may

have on the results; (4) that the duration of AEs is specified to be known without any uncertainty; and (5) duration of 5L treatments were estimated from an external source. The ERG believes that amending these limitations is unlikely to affect the central estimate of the ICERs of IsaPd compared with Pd and PanVd.

(8) Uncertainty in the clinical evidence

The ERG comments that the comparison of efficacy between IsaPd and PanVd had to be conducted using an MAIC which will, as acknowledged by the company, have inherent limitations, primarily in ensuring that the matching undertaken is appropriate and that no unobserved confounders exist. In addition to this the company assume: that the treatment effect was constant over time, no interaction between treatment and line of therapy; and apply a hazard ratio to a non-proportional hazards model. The fact that ICARIA-MM was open-label may have introduced measurement bias, and may have altered patterns of oral medication use. The use of a post hoc group to generate the relative efficacy of IsaPd compared to Pd would not have the protection of randomisation, however, as baseline demographics and clinical characteristics were similar between the 4L patients and the full population and clinicians did not believe the relative efficacy to differ by line of treatment the analyses were believed suitable for decision making.

4.4 ERG's exploratory analyses

This section presents the methods and results of the ERG's exploratory analyses undertaken using the company's model.

4.4.1 Overview of the ERG's exploratory analyses

The ERG undertook exploratory analyses to address the key points identified within the critical appraisal (Section 4.3.3). These included correcting the errors identified in the company's model and amending assumptions. The exploratory analyses were combined to form the ERG's preferred base case analysis.

The ERG also undertook additional sensitivity analyses using the ERG's preferred base case model to explore the impact of: adopting different survival models for OS, PFS and TTD; assuming no drug wastage; and assuming 100% RDI for all 4L drugs.

Implementation of the ERG's exploratory analyses was repeated by a second member of the ERG to ensure that the results are free from errors. Technical details regarding the implementation of these analyses in the company's model are presented in ERG Appendix 1.

4.4.2 ERG exploratory analysis – methods

ERG preferred base case analysis

The ERG's preferred base case analysis is comprised of two sets of amendments to the company's model; these are detailed below.

ERG exploratory analysis 1: Correction of perceived error within the company model

The ERG made corrections to the company's model, by: (i) changing the formulae in each of the intervention and comparators' calculations worksheets such that the negative QALY values associated with deteriorating health at the end of life are added rather than subtracted from the overall QALY gains; and (ii) amending the formulae used to calculate dexamethasone administration costs for IsaPd and Pd to reflect the weighting between IV and oral administration.

ERG exploratory analysis 2: Extending the time horizon of the model

The ERG explored the impact on the ICER of extending the time horizon to 20 years which was the maximum time horizon within the model. At this point 0.7% of patients were alive in the IsaPd group and 0.0% alive in the Pd and PanVd groups.

ERG exploratory analysis 3: ERG's preferred base case

The ERG's preferred base case includes ERG exploratory analysis 1 and 2.

Additional sensitivity analyses using the ERG preferred model

The following additional sensitivity analyses were undertaken using the ERG's preferred model ("ERG exploratory analysis 3: ERG's preferred base case"). It is acknowledged that many functions could be used when fitting the data; for brevity, the ERG has selected two distributions which had relatively low BIC values and which have different properties in terms of hazard rates across time to provide an indication of the range of uncertainty within the ICER.

ERG additional sensitivity analysis 1: Use of alternative models for OS

Based on similar BIC values, see Figure 5, in Section 4.2.4.2.1, the ERG assessed the impact on the ICER if the jointly-fitted lognormal or the jointly-fitted Weibull distributions were used instead of the exponential distribution for OS.

ERG additional sensitivity analysis 2: Use of alternative models for TTD

Based on similar BIC values, see Figure 13, in Section 4.2.4.2.3, the ERG assessed the impact on the ICER if the jointly-fitted log-logistic or the jointly-fitted Weibull distributions were used instead of the exponential distribution for TTD.

ERG additional sensitivity analysis 3: Use of alternative models for PFS

Based on clinical advice provided to the company, the ERG assessed the impact on the ICER if the exponential or the jointly-fitted Weibull distributions were used instead of the jointly-fitted lognormal distribution for PFS. The ERG notes that the BIC for the jointly-fitted Weibull distribution, see Figure 9, in Section 4.2.4.2.2, is approximately seven more than the jointly-fitted lognormal, as such, the jointly-fitted Weibull model may not fit the observed data as well as the jointly-fitted lognormal.

ERG additional sensitivity analysis 4: No wastage considered

The ERG explored the impact of assuming no drug wastage.

ERG additional sensitivity analysis 5: Setting all RDIs to 100%

The ERG explored the impact of assuming that all reductions in dose intensities were not pre-planned and were associated with drug wastage. The ERG acknowledges that this sensitivity analysis is extreme but believes it provides useful information to the committee.

Limitations not amended by the ERG

The company's model is subject to a number of limitations which impact on the reliability of the ICERs generated from it. The following aspects of the model were not amended by the ERG:

Limitation 1: Potentially inaccurate estimation of drug acquisition and administration costs

The ERG did not have time to adjust the model to ensure that the costs of drug acquisition and administration related to the number of people who would receive the drug. The ERG anticipates that amending this error would slightly increase the ICER for IsaPd.

Limitation 2: Drugs assumed to be used in 5L that would not be used in England

The ERG acknowledges that the survival of patients may be influenced by the drugs that were used in 5L, as such removal of these costs without adjusting survival would be inappropriate. The ERG cannot predict with confidence the impact on the ICER for IsaPd if only drugs recommended in England were used in the ICARIA-MM study.

Limitation 3: Potential face validity violations in the utilities sampled within the PSA

The ERG does not anticipate that removing this limitation would markedly change the ICER but notes that the current sampling methodology is likely to increase the uncertainty within the PSA.

Limitation 4: Underestimation of uncertainty in the decision problem

The ERG did not have time to conduct further work to reduce the level of uncertainty. Whilst the ERG believes that it is likely there would be a small increase in the probabilistic ICER due to the increased uncertainty this cannot be predicted with certainty.

Limitation 5: Uncertainty in the clinical evidence

The ERG could not reduce the uncertainty in the clinical evidence.

4.4.3 ERG exploratory analysis – results

4.4.3.1 *IsaPd vs Pd*

ERG preferred base case analysis results

Table 17 presents the results of the ERG's preferred analysis. As shown in the table, correcting the errors in the company's deterministic model increases the ICER for from £118,816 to £126,611 per QALY gained, whilst increasing the time horizon to 20 years decreases the ICER to £115,996. The ERG's preferred probabilistic base case ICER for IsaPd versus Pd is estimated to be £133,461 per QALY gained.

Table 17: ERG exploratory analysis results: IsaPd vs Pd

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER
Company's base case							
IsaPd	[redacted]	[redacted]	[redacted]	1.649	1.071	£127,267	**£118,816**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 1: Correction of errors							
IsaPd	[redacted]	[redacted]	[redacted]	1.649	1.076	£136,269	**£126,611**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 2: Extending the time horizon to 20 years							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.098	£127,363	**£115,996**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic ERG preferred base case (ERG analyses 1 and 2 combined)							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.102	£136,364	**£123,769**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
Probabilistic ERG preferred base case (ERG analyses 1 and 2 combined) – 1000 iterations							
IsaPd	[redacted]	[redacted]	[redacted]	1.692	1.102	£147,041	**£133,461**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year

Table 18 details the results of the ERG's additional sensitivity analyses. The sensitivity analyses applied to the ERG-preferred base case resulted in an ICER range for IsaPd compared with Pd of £103,095 to £213,105 per QALY gained. The lower value of the range reflects a scenario in which no drug wastage is assumed, whilst the upper value of the range relates to the use of a jointly-fitted log-

logistic model for TTD. The ICER also appeared sensitive to the choice of survival model used for OS, although it was insensitive to the model used for PFS.

Table 18: ERG additional sensitivity analyses: IsaPd vs Pd (all deterministic)

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER
ERG's preferred base case							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.102	£136,364	**£123,769**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 1a: Use of a jointly-fitted lognormal model for OS							
IsaPd	[redacted]	[redacted]	[redacted]	1.701	1.108	£136,387	**£123,041**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 1b: Use of a jointly-fitted Weibull model for OS							
IsaPd	[redacted]	[redacted]	[redacted]	1.144	0.769	£135,279	**£176,028**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 2a: Use of a jointly-fitted log-logistic model for TTD							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.102	£234,792	**£213,105**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 2b: Use of a jointly-fitted Weibull model for TTD							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.102	£140,050	**£127,115**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 3a: Use of an exponential model for PFS							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.091	£136,364	**£124,987**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 3b: Use of a jointly-fitted Weibull model for PFS							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.080	£136,364	**£126,281**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 4: No wastage considered							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.102	£113,586	**£103,095**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 5: Setting all RDIs to 100%							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.102	£148,663	**£134,932**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year

4.4.3.2 *IsaPd vs PanVd*

ERG preferred base case analysis results

Table 19 presents the results of the ERG's preferred analysis for IsaPd versus PanVd. As shown in the table, correcting the errors in the company's model increases the ICER from £216,856 to £215,793 per QALY gained. The ERG's preferred base case ICER for IsaPd versus PanVd is estimated to be £238,300 per QALY gained.

Table 19: ERG exploratory analysis results, IsaPd vs PanVd

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER
Company's base case							
IsaPd	[redacted]	[redacted]	[redacted]	1.144	0.849	£184,053	**£216,856**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 1: Correction of errors							
IsaPd	[redacted]	[redacted]	[redacted]	1.144	0.853	£184,053	**£215,793**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 2: Extending the time horizon to 20 years							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.873	£184,140	**£210,812**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic ERG preferred base case (ERG analyses 1 and 2 combined)							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.876	£184,140	**£210,102**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
Probabilistic ERG preferred base case (ERG analyses 1 and 2 combined) – 1000 iterations							
IsaPd	[redacted]	[redacted]	[redacted]	1.104	0.825	£196,603	**£238,300**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year

Table 20 details the results of the ERG's additional sensitivity analyses. The sensitivity analyses applied to the ERG-preferred base case resulted in an ICER range for IsaPd versus PanVd of £141,814 to £365,613 per QALY gained. The lower value of the range reflects a scenario in which no drug wastage is assumed, whilst the upper value of the range relates to the use of a jointly-fitted log-logistic model for TTD. The ERG notes that in the latter analysis, the increase in treatment time for PanVd is curtailed by the maximum treatment duration of 48 weeks for this intervention. The ICER also appeared sensitive to the choice of model used for OS, although it was insensitive to the model used for PFS.

Table 20: ERG additional sensitivity analyses: IsaPd vs PanVd (all deterministic)

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER
ERG's preferred base case							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.876	£184,140	**£210,102**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 1a: Use of a jointly-fitted lognormal model for OS							
IsaPd	[redacted]	[redacted]	[redacted]	1.575	1.119	£184,925	**£165,233**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 1b: Use of a jointly-fitted Weibull model for OS							
IsaPd	[redacted]	[redacted]	[redacted]	0.789	0.633	£183,360	**£289,568**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 2a: Use of a jointly-fitted log-logistic model for TTD							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.876	£320,436	**£365,613**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 2b: Use of a jointly-fitted Weibull model for TTD							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.876	£189,351	**£216,046**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 3a: Use of an exponential model for PFS							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.853	£184,140	**£215,967**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 3b: Use of a jointly-fitted Weibull model for PFS							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.834	£184,140	**£220,920**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	
ERG sensitivity analysis 4: No wastage considered							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.876	£167,529	**£191,148**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 5: Setting all RDIs to 100%							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.876	£196,441	**£224,136**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year

The company does not believe that PanVd is a comparator in 4L treatment as it is rarely used due to toxicity reasons; as stated in Section 2.3.3 this opinion was not universally supported by the clinical advisors to the ERG.

The ERG notes that if a full incremental analysis was considered appropriate, PanVd dominates Pd and the ICER for IsaPd would be that compared with PanVd. On investigation, it was determined that the reason PanVd was assumed to be less expensive than Pd, despite providing more health gains, was that the estimated TTD was markedly lower on average in the PanVd arm compared with the Pd arm. However, the limitations of the MAIC need to be considered when evaluating the comparison of Pd and PanVd.

4.5 Discussion

The model submitted by the company was perceived to have few errors and therefore the deterministic ICERs for IsaPd compared with Pd were similar between the company's estimate

(£118,816 per QALY gained) and the ERG's estimate (£123,769 per QALY gained). Probabilistic analyses were seen to increase the ICER to £133,461 per QALY gained compared with Pd within the ERG's preferred base case. Sensitivity analyses indicated that the ICER for IsaPd compared to Pd was unlikely to be below £100,000.

The ICER for IsaPd compared with PanVd was higher than when Pd was the comparator; for this comparison, the deterministic ICERs were £216,856 per QALY gained (company) and £210,102 per QALY gained (ERG). Again, the probabilistic estimate was higher than the deterministic analysis; the ERG's estimate was £238,300 per QALY gained. Sensitivity analyses indicated that the ICER for IsaPd compared to Pd was unlikely to be below £140,000. However, there is considerable uncertainty in the ICER as the comparison was informed by a MAIC which may have multiple limitations. However, the ERG believes it highly unlikely that the cost per QALY would fall below £50,000 per QALY gained.

The appropriate ICER for IsaPd depends on whether it is believed that PanVd is an appropriate comparator; the company states that it is rarely used due to toxicity reasons. However, as stated in Section 2.3.3, there was mixed agreement amongst the clinical experts advising the ERG. If all treatments are considered appropriate then PanVd is expected to dominate Pd.

Finally, the ERG comments that these results do not include the PAS discounts for pomalidomide, panobinostat and lenalidomide and thus the ICERs presented here may be misleading. The cost per QALY gained for IsaPd compared with Pd and for IsaPd compared with PanVd when the PAS discounts are incorporated into the analysis are provided in a confidential appendix to this ERG report.

5 END OF LIFE

NICE end of life supplementary advice should be applied in the following circumstances and when both the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The following paragraphs summarise the evidence presented in the CS to support the company's position that IsaPd meets NICE's end of life criteria. Further information is provided in Table 32 of the CS.[3]

Short life expectancy criterion

In Table 32 of the CS,[3] the company cites precedent within NICE appraisals that the appraisal committee accepted that the end of life criteria were met when appraising pomalidomide (TA427)[26] at 3L and when appraising daratumumab (TA510) at 3L.[56] The company additionally states that the both Pd and PanVd have reported median OS times of less than 2 years. However, the ERG comments that the company's model predicted that the probabilistic (deterministic) estimate for mean survival for those on Pd was [redacted] years ([redacted] years). For patients receiving PanVd, these values were [redacted] ([redacted]) years. Given these values, it is not certain that the short life expectancy criterion is met.

Life extension criterion

In Table 32 of the CS,[3] the company states that "*Overall survival data are not yet mature. However, in the ITT population, at approximately 1 year of follow-up, a trend toward longer OS for IsaPd vs Pd alone, with an early separation of the survival curves (Figure 15), was observed (HR=0.687; [95% CI; 0.461, 1.023]).*

At the time of the analysis, the probability of surviving (95% CI) 12 months was 0.720 (95% C; 0.636, 0.787) in the IsaPd arm and 0.633 (95% CI; 0.545, 0.709) in the Pd arm." Based on the company's model, it is predicted that IsaPd will increase life expectancy by 1.628 years compared with Pd and by 1.056 years compared with PanVd, although the gain compared with PanVd is uncertain due to the comparison being informed by the MAIC. Given these values, the ERG agrees that it is likely that the criterion for extension to life is met.

6 OVERALL CONCLUSIONS

The main source of evidence in the CS was one open-label RCT of IsaPd for treating RRMM. Median PFS was greater in the IsaPd arm than the Pd arm among RRMM patients at 4L (HR 0.598 [95%: CI 0.348, 1.030], *p*=0.0611), and there was a trend towards superiority in OS in the IsaPd arm (HR 0.494 [95% CI 0.240, 1.015], *p*=0.0502), although the data were immature. IsaPd appears to be generally well tolerated. Whilst the study was generally well reported, there are limitations relating to its unblinded nature, post-hoc analysis of the 4L population and inconsistency between subsequent treatments in the study and in the current UK clinical management pathway.

IsaPd and PanVd were not part of a connected network of evidence and were compared using a MAIC of IsaPd from the ICARIA-MM study and PanVd from the PANORAMA-2 study. The results appeared favourable to IsaPd with a HR of 0.369 (95% CI 0.259 to 0.526) for PFS, and a HR of 0.642 (95% CI: 0.380, 1.082) for OS. As acknowledged by the company, the MAIC is subject to limitations; it is not clear whether the covariates represent all relevant prognostic factors and/or treatment effect modifiers and the final comparison may be biased. The company believes that PanVd is not an appropriate comparator as it is rarely used in 4L treatment due to its toxicity. As stated in Section 2.3.3 this view was not universally supported by clinical advice provided to the ERG. As such, the ERG believes that the company's secondary analyses will be appropriate for a proportion of patients who would receive PanVd rather than Pd.

The company submitted an economic model which indicated that the probabilistic cost per QALY gained of IsaPd compared with Pd was £130,321 and was £248,197 compared with PanVd. The ERG amended two perceived modelling errors and lengthen the time horizon from 15 years to 20 years. These amendments resulted in ICERs of £133,461 per QALY gained for IsaPd compared with Pd and of £238,300 per QALY gained for IsaPd compared with PanVd. Scenario analyses conducted by the ERG indicated that the ICER for IsaPd compared with Pd was unlikely to be below £100,000 and that the ICER for IsaPd compared with PanVd was unlikely to be below £140,000 per QALY gained. However, these values do not include PAS discounts related to pomalidomide, panobinostat or lenalidomide; results including these PAS discounts contained in a confidential appendix to this report.

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8. APPENDICES

Appendix 1: Technical appendix – instructions for implementing the ERG's exploratory analyses within the company's model

ERG exploratory analysis 1: Correction of errors

In the company's model:

(i) In worksheets 'Comp1 Calc', 'Comp2 Calc' and 'Comp3 Calc' of the company's model, replace the formula in cell FD29 with the formula "=IFERROR((DH29*IF(util.gp_apply="Yes",MIN(comp1.offtxPPS_util,FL29),comp1.offtxPPS_util)+SUM(DK29:INDEX(DK29:DK1072,util.term_duration))*comp1.term_util)*7/days_per_year,0)". Drag the formulae down to row 1072.

(ii) In worksheet 'Comp1 Calc', include in the end of the formulae in cells ED29, EE29, EF29 and EG29, respectively, the terms '*(0.745098039215686)*(1-0.135)', '*(1-0.745098039215686)*(1-0.135)', '*(0.745098039215686)*(0.135)', and '*(1-0.745098039215686)*(0.135)'. Drag each of these formulae down to row 1072.

(iii) In worksheet 'Comp2 Calc', include in the end of the formulae in cells EB29, EC29, ED29 and EF29, respectively, the terms '*1*0.155', '*0*0.155', '*1*(1-0.155)', and '*0*(1-0.155)'. Drag each of these formulae down to row 1072.

ERG exploratory analysis 2: Extending the time horizon of the model

In the company's model, go to worksheet 'Settings', cell H7, and replace value with "20".

ERG exploratory analysis 3: ERG's preferred base case

The ERG's preferred base case includes ERG exploratory analysis 1 and 2; therefore, apply all the changes listed above.

All sensitivity analyses undertaken by the ERG were applied separately to the ERG's preferred base case version of the model.

ERG sensitivity analysis 1: Use different functions to extrapolate OS data

In the company's model go to worksheet 'SelectDist_OS' and change all the curve selections in the dropdown menu in cells E9:G9, E10:G10 and E11:G11:

a. select, respectively, the options 'OS: IsaPd Lognormal (R)', 'OS: Pd Lognormal (R)' and 'OS: IsaPd Lognormal (R)'.

b. select, respectively, the options 'OS: IsaPd Weibull (R)', 'OS: Pd Weibull (R)' and 'OS: IsaPd Weibull (R)'.

ERG sensitivity analysis 2: Use different functions to extrapolate TTD data

In the company's model go to worksheet 'SelectDist_TTD' and change all the curve selections in the dropdown menu in cells E9:G9, E10:G10 and E11:G11:

a. select, respectively, the options 'TTD: IsaPd Log-Logistic (R)', 'TTD: Pd Log-Logistic (R)' and 'TTD: IsaPd Log-Logistic (R)'.
b. select, respectively, the options 'TTD: IsaPd Weibull (R)', 'TTD: Pd Weibull (R)' and 'TTD: IsaPd Weibull (R)'.

ERG sensitivity analysis 3: Use different functions to extrapolate PFS data

In the company's model go to worksheet 'SelectDist_PFS' and change all the curve selections in the dropdown menu in cells E9:G9, E10:G10 and E11:G11:

a. select, respectively, the options 'PFS: IsaPd Exponential', 'PFS: Pd Exponential' and 'PFS: IsaPd Exponential'.
b. select, respectively, the options 'PFS: IsaPd Weibull (R)', 'PFS: Pd Weibull (R)' and 'PFS: IsaPd Weibull (R)'.

ERG sensitivity analysis 4: Assumption of no drug wastage

In the company's model, go to worksheet 'Costs_MedAdmin', cell E6, and change the option in the dropdown menu to 'No'.

ERG sensitivity analysis 5: Assumption of all reductions in dose intensities were not pre-planned

In the company's model, go to worksheet 'Regimen', cells K9:K17, K19:K24 and K29:K34, and replace values with "100%".

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [ID1477]

You are asked to check the ERG report 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 5 February** using the below 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 committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Minor error in reporting of company response to ERG clarification questions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
There is a minor error in Section 3.2.1.4, page 24, paragraph 3 of the ERG report to NICE. The report states that: *"The company's clarification response question A6[7] indicates that the 4L post hoc analysis used data on patients at 4L from the ITT population (rather than the safety population)."*	This response was to clarification question number A5, not A6. The correct version should say: *"The company's clarification response question A5[7] indicates that the 4L post hoc analysis used data on patients at 4L from the ITT population (rather than the safety population)."*	The correction will enable consistency in the reporting between documents that will be published by NICE, post-appraisal committee meeting.	The text has been changed to the proposed amendment.

Issue 2 Minor spelling error of study name

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Spelling error of study name in Section 3.2.1.6, page 29, paragraph 2 of the ERG report to NICE. The additional study is referred to in the ERG report as 'IKEMIA'.	This should be corrected to 'IKEMA'.	Factual accuracy	The text has been changed to the proposed amendment.

Issue 3 Incorrect reporting regarding median duration of follow-up from trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect reporting in Section 3.2.4, page 31, paragraph 3 regarding median duration of follow-up. The ERG report states that: *"The median duration of follow-up was not reported in the CS"*	Please amend to: *'The median duration of follow up is reported on page 57 of the company submission'*	Factual accuracy	The text has been changed to "The median duration of follow-up was reported in the CS as being 11.56 and 11.73 (for OS) (CS, page 57)"

Issue 4 Misleading statement reporting hazard ratios for ITT and 4L populations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The following statement in Section 3.2.4.2, page 33, paragraph 1 is misleading as it mixes the ITT and 4L populations: *"Data for the ITT population of ICARIA-MM are reported in the CS, (pages 54-55);[3] the stratified (by age) HR was 0.494 (95% CI: 0.240, 1.015)."*	Please amend to read: *'Data for the ITT population of ICARIA-MM are reported in the CS, (pages 57-59);[3] the stratified (by age) HR was 0.687 (95% CI; 0.461, 1.023). The HR observed in the 4L population was 0.494 (95% CI: 0.240, 1.015).'*	Factual accuracy	Upon further checking, the HR in the ORR section (3.2.4.2) relates to OS and not ORR, and so this second clause has been deleted.

Issue 5 Incorrect reference to medicinal product

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.1, page 49, paragraph 1 refers to acid acetilsalycilic	Should be corrected to 'acetylsalicylic acid'	Factual accuracy	The text has been changed to the proposed amendment.

Issue 6 Model structure was not changed post clarification questions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In section 4.2.2, page 49, paragraph 5, the ERG notes that *"the original approach adopted by the company was chosen in preference to a more conventional three-state model in order to allow for the use of different utility values for patients conditional on whether people were on or off treatment. During the clarification process,[7] the company adopted an alternative approach to calculating the health state QALYs, where utility in the PFS and PD health states was assumed to be independent of whether or not the patient is on treatment".*	Whilst it is noted in an earlier section, section 1.4, page 10, paragraph 4, that *"the model structure remained unaltered following the clarification process"*, we would like to ensure consistency and clarity in the reporting. We suggest amending the wording to read: '….*During the clarification process,[7] the company adopted an alternative approach to calculating the health state QALYs, where utility in the PFS and PD health states was assumed to be independent of whether or not the patient is on treatment. However this did not constitute a formal change to model structure.'.*	It should be noted that this was a change in the parameters used, not the model structure. The utility for Off treatment PFS and PD health states was assumed to be equal in the amended model. However, the structure that allows for different utilities to be included remains.	Not a factual error, but the text added to minimise ambiguity.

Issue 7 Inconsistent reporting 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In section 4.2.2, page 50, paragraph 4, ERG notes that: *"The model does not include any QALY loss associated with Grade 3/4 AEs for IsaPd or Pd."*	We suggest the following wording: *'The model does not explicitly include any QALY loss associated with Grade 3/4 AEs for IsaPd or Pd however the company assumes that utility decrements are likely to be captured in the EQ-5D assessment.'*	The model does not ***explicitly*** account for effects of AEs on utility values but does so ***implicitly*** to the extent that the effect of AEs are captured in EQ-5D assessments. This clarification is made later in the report (section 4.2.4.3, page 65, paragraph 1), and it is respectfully recommended that the clarification is added to the statement in the earlier sections of the report	Text has been added to make this point.

Issue 8 Inconsistent reporting 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In section 4.2.3, page 51, paragraph 3, the ERG noted: *"HRQoL is assumed to be conditional on two factors: (i) whether a patient is in PFS or PPS, and (ii) which 4L treatment was received, based on estimates derived from the GEE model fitted to the data collected in ICARIA-MM."*	We suggest the following wording: *'HRQoL is assumed to be conditional on two factors: (i) whether a patient is in PFS or PPS (although in the revised model these were set to be the same), and (ii) which 4L treatment was received, based on estimates derived from the GEE model fitted to the data collected in ICARIA-MM."*	The model structure allows for utilities to vary by on versus off treatment although these are set to be the same in the revised base case. Later in this report, the ERG notes that overall model structure has not been adapted and, rather, that the same utility values are used for the on and off treatment states by PFS or PPS.	Text has been added to improve clarity.

Issue 9 Clarity on adverse event disutility

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Table 6, page 56, row 13, AE disutility- IsaPd and Pd. The ERG states "*Not included. The company assumed that the utility values for PFS in ICARIA-MM captured the effects of AEs on HRQoL".*	We suggest the following wording: *'Not explicitly included. The company assumed that the utility values for PFS in ICARIA-MM captured the effects of AEs on HRQoL".*	See issues 7 and 8 above.	The requested change has been made.

Issue 10 Minor inaccuracy in reporting

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.4.1 – mean body weight for population listed as 73.13 kg	Weight should be changed to 73.14 kg	Minor edit to ensure accuracy in reporting	The requested change has been made.

Issue 11 Misleading statements can lead to incorrect interpretation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG noted in section 4.2.4.2, page 55, paragraph 4: *"The company fitted the same models to each arm of the ICARIA-MM study, partly to allow estimation of a single treatment effect. However, this approach assumes that the treatment effect is*	We suggest the following wording: *"The company explored two alternative approaches for modelling treatment effects: (1) "restricted" models in which only 1 parameter for each distribution is allowed to vary by treatment; and, (2) "unrestricted" distributions in which <u>all</u> parameters for each distribution were*	This amendment helps to clarify that the approach of varying parameters was used.	We have not changed the original text but have added: "To relax this assumption, the company also fitted separate but identical models to each treatment arm."

constant over time on some appropriate scale (i.e. proportional hazards, acceleration failure or proportional odds). While this approach is a convenient modelling assumption for estimating a treatment effect, there is no stated clinical reason why the treatment effect should be constant over time. Making this assumption when the treatment effect is not constant will generate biased estimates of population mean survival."	*allowed to vary by treatment. With approach (1), the treatment effect is assumed to be constant over time. For approach (2), the treatment effects are not so constrained."*		

Issue 12 Misleading statements can lead to incorrect interpretation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Section 4.2.4.2, page 55, paragraph 5, the ERG noted: "Section B.3.3 of the CS states that "*the RCS distributions have six parameters, not including the knots*". However, a proportional hazards restricted cubic spline model with a single covariate representing a constant treatment effect and including a single knot is: $\ln[H(t;z_1)] = \gamma_0 + \gamma_{10}x + \gamma_{20}v_1(x) + \beta_1 z_1$ Thus, a proportional hazards model including one knot has four parameters, while a non-proportional hazards model including a single knot would have six parameters. Hence, it is not clear to what parameters the company is	We suggest the following wording should also be included: *'An RCS Weibull, log-logistic, or lognormal distribution with one knot has three parameters per treatment group excluding the knots and six parameters per treatment group including the knots (there are 3 knots [the same for both treatment groups] based on the minimum, median, and maximum failure times for both groups combined).'*	Amended text is provided to increase clarity.	Not a factual error.

referring.”			

Issue 13 Minor editorial errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Section 4.2.4.2, page 55, paragraph 6, ERG noted: “*As shown in Sections 4.2.4.2.1 and 4.2.4.2.2, the results of the MAIC may appear to lack face validity as PanVd is estimated to have a shorter time to progression than Pd, but is estimated to have a shorter survival.”*	Edit section numbers described here to refer to 3.4.1 and 3.4.2	Factual accuracy. It does not appear as if sections 4.2.4.2.1 and 4.2.4.2.2 provide details of the MAIC for PanVd.	The text has been amended with the HRs added to make the point clearer. The cross reference has been removed.

Issue 14 Additional clarification needed

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Section 4.2.4.2.1, page 55-56, last paragraph, ERG noted: “*Section B.3.3 of the CS refers to restricted cubic spline Weibull, lognormal and log-logistic models. However, it is not clear to the ERG what is meant by this. Weibull, lognormal and log-logistic models can be parameterised using a restricted cubic spline approach depending on the link function used*	We suggest the ERG report text is amended to provide the additional clarification and corrections as explained in the “Justification for amendment” column.	We offer the following explanation for clarity: The RCS distributions are estimated using the FlexSurv package in R. The default parameterization for the RCS distributions estimated by FlexSurv uses a Weibull distribution with the scale parameter set to “hazard”. The log-logistic and	Not a factual error. The ERG is still not clear what is meant by restricted cubic spline Weibull, lognormal and log-logistic models, and the amendment does not clarify this. The scale on which parameter are estimated should not make a difference

and by including no additional knots. These analyses should give the same results as for standard parameterisations of these models."		lognormal distributions are estimated in FlexSurv by setting the scale parameter to "odds" and "normal", respectively. These alternative parameterizations of the RCS distributions are described in the FlexSurv documentation. It should be noted that the RCS log-logistic and RCS log-normal distributions *do not* yield the same results as the conventional parameterizations of these distributions.	but adding knots will change the meaning of a model.

Issue 15 Misleading statements can lead to incorrect interpretation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 63, paragraph 1, ERG noted: *"Summary plots for the chosen fit to OS, PFS, PFS on treatment and TTD were provided in Figures 37 to 40 of the CS, although PFS on treatment is no longer used in the company's revised model. The ERG is cautious regarding whether these plots are correct, as in the clarification process (question B6)[7] it was acknowledged that Figure 37 was incorrect and the ERG identified later that the projections of TTD using an*	The TTD plots included in the Excel Model are correct. The values in Figures 37 to 40 of the CS are incorrect. Although the utility value was modified so that the same utility value is assumed for PFS on treatment and PFS off treatment, the PFS is still portioned into "on" and "off" treatment states in the model. In light of this, we suggest **removing** the following text: *"although PFS on treatment is no longer used in the company's revised model"*	Thank you for noting the discrepancies. There does appear to have been a transposition issue with copying the figures included in the model into the report. The data in the report have been re-checked and are correct. The clarification regarding PFS on treatment should be made because the structure of the model has not been changed.	We have removed the text as requested and have added a statement that the company has confirmed that Figures 37 to 40 of the CS were incorrect.

exponential function appear different between Figures 35 and 39, with the ERG suspecting Figure 39 is erroneous."			

Issue 16 Additional clarification needed

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 64, paragraph 1, the ERG noted: *"It is not clear why in Table 58 of the CS[3] the company refers to bootstrapping or whether the analyses that were done allow for correlation between parameters."*	We suggest the ERG report text is amended to provide the additional clarification and corrections as explained in the "Justification for amendment" column.	We offer the following explanation: The reference to bootstrapping indicates that the parameters were sampled from the joint bootstrap distribution of the parameter estimates derived by sampling with replacement from the ICARIA-MM trial and rerunning the estimation procedure for each bootstrap replicate. This approach ensures that the parameter estimates are correlated not only within distributions but also across outcome and other parameter estimates. While it is possible to sample parameters of the distributions from the multivariate normal distribution based on the estimated variance-covariance matrices to ensure the appropriate correlation of parameters within distributions for individual	Sentence deleted.

		outcomes, this approach does not ensure the correlation of parameters across outcomes. This is problematic as PFS, OS and TTD are all likely to be highly correlated. Sampling from the joint bootstrap distributions of these parameters ensures appropriate correlation within distributions and across outcomes.	

Issue 17 Additional clarification needed

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 70, paragraph 4, "*The ERG notes some discrepancies between the revised values reported by the company for the rates of patients receiving GCSF, blood and platelet transfusions and the number of these procedures received per patient in the clarification response (clarification response B19, Table 20)*[7] *and the updated submitted model. Additionally, the ERG notes that these rates for patients receiving PanVd have changed between the original submission and the clarification with no reason provided. It is not clear which data were intended to be	We suggest the ERG report text is amended to provide the additional clarification and corrections as explained in the "Justification for amendment" column.	It is important that the reviewers have sufficient information for determining which data the company intends to use and the rationale behind the edits during the clarification process. Therefore we offer the following explanation: Rates of patients receiving GCSF, blood and platelet transfusions and the numbers of these procedures received per patient for those receiving IsaPd and Pd were edited during the clarification process as recommended by the ERG. The values used are highlighted in clarification response B26. To allow for incorporation of different numbers of administrations by	Text added to the document to provide the company rationale.

used by the company."		treatment, the model had been amended during the clarification process.	

Issue 18 Additional clarification needed

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The following two items: Page 83, bullet point 6 • Within the PSA it was possible that the sampled mean utility for patients in progressed disease could be higher than that for patients in PFS; the ERG does not believe this to be plausible. The ERG believes that amending this limitation is unlikely to affect the central estimate of the ICERs of IsaPd compared with Pd and PanVd. Page 86, paragraph 7 • **Limitation 3: Potential face validity violations in the utilities sampled within the PSA** The ERG does not anticipate that removing this limitation would markedly change the ICER but notes that	We request that the ERG report text should provide a complete picture of the evidence as explained in the justification for amendment column.	As noted in company responses to the ERG questions, the utility values were sampled from the bootstrap distribution of parameter estimates. Accordingly, the utility values across states are based on the same sample and regression equations within bootstrap samples. This ensures general consistency of the utility values across states (and treatments) within each sample. While it is possible that the utility values for PPS could be higher for PFS in the simulations, this could also have been true for the actual sample. We believe that the statement that utility values in the PSA may lack face validity is factually inaccurate and that this clarification is an important point for consideration while reviewing the results of the model. We do not believe there is	No change has been made. The ERG maintains its position that we do not believe it plausible that, on average, the utility for patients in progressed disease is higher than that for patients in non-progressed disease. Whilst the ERG acknowledges that for some individual patients this may be the case, we do not believe this would be true, on average, if a very large sample size were available. In the large number of oncology appraisals that ERG members have been involved with (n>40) we have never seen progressed disease with a higher midpoint utility than progression-free disease, and have repeatedly heard clinical testimonies of the disutility associated with

the current sampling methodology is likely to increase the uncertainty within the PSA		evidence to support that modification of the method would increase the uncertainty in the PSA.	progression. Use of words such as 'potential' and 'may' lead to this point not being a factual error, but a difference of opinion between groups. The ERG believes that uncertainty will be increased due to the utility values in the company's PSA. We would be happy to discuss this at the Appraisal Committee, although this may not be seen as important given i) the lack of alternative results and ii) the ERG's belief that the central estimate will be largely unchanged.

Issue 19 ***Inaccurate reporting in the ERG report***

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Discussion section: "Probabilistic analyses were seen to increase the ICER to £238,300 per QALY gained within the ERG's preferred base case."	Please amend to: "Probabilistic analyses were seen to increase the ICER to £133,461 per QALY vs. Pd gained within the ERG's preferred base case."	This appears to be a typographical error in which the value for PanVd was taken instead of that for Pd.	Text amended as suggested

(please cut and paste further tables as necessary)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [ID1477]

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: March 2020

1. Topic background

Commonly used abbreviations

PANO/BORT/DEX (PanVd in company and ERG documents)	panobinostat, bortezomib, dexamethasone
POM/DEX (Pd in company and ERG documents)	pomalidomide, low dose dexamethasone
Intervention: ISA/POM/DEX (IsaPd in company and ERG documents)	Isatuximab, pomalidomide, low dose dexamethasonebortezomib,

1.1 Disease background

- Multiple myeloma (MM) is a malignant, progressive and incurable haematopoietic tumour of plasma cells, characterised by the neoplastic proliferation of clonal plasma cells that produce monoclonal immunoglobulins.
- People with MM report a high symptom burden which impacts patients' quality of life (QoL), as well as that of families or carers.
- MM is characterised by cycles of remission and relapse. In general, patients diagnosed with MM will receive 4 to 8 different regimens. However, once a patient becomes refractory to those agents, their survival is limited, and they would welcome newer treatment options.
- Multiple myeloma is incurable. Treatment aims to prolong survival and maintain a good quality of life by controlling the disease and relieving symptoms. If the disease progresses after initial treatment, the choice of subsequent therapy is influenced by previous treatment and response to it, duration of remission, comorbidities and patient preference.

Patient perspective (Submission from Myeloma UK**)**

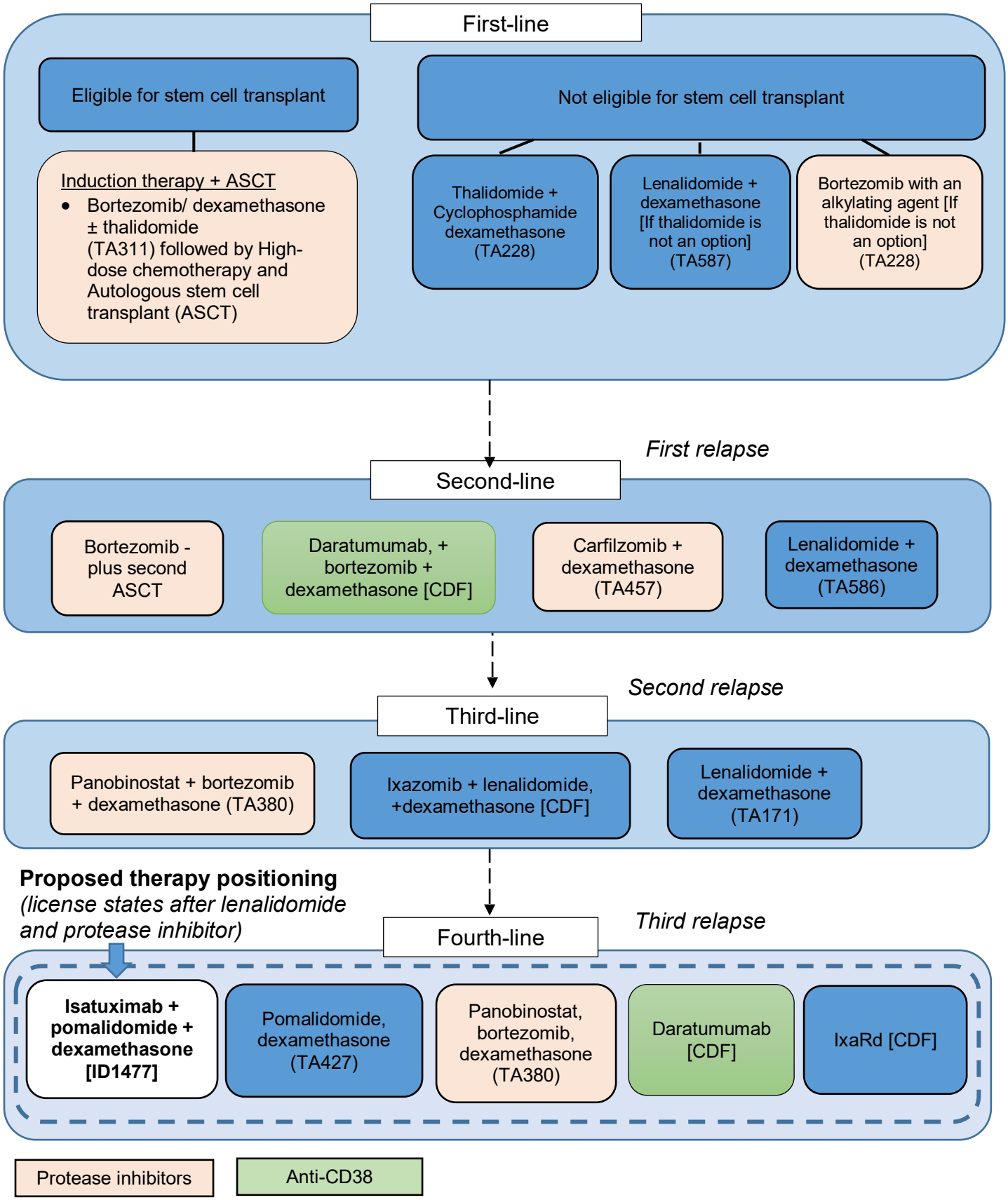
- Treatments which can halt disease progression can improve quality of life.
- Complications of myeloma can be significant and include severe bone pain, bone destruction, kidney damage, fatigue and a depleted immune system.
- Disease burden is often even more significant for people who experience multiple relapses.
- Impact on carers is significant and challenging.

- A range of treatment options with different mechanisms of action at each stage of the pathway is vital for myeloma patients.
- Current unmet need. Treatment options limited by further relapses.
- Patients tend to prefer oral treatments over intravenous infusions but there are also patients who welcome their treatment being delivered in the safety of a hospital.

Professional organisation perspective (submission from UK Myeloma Forum)

- Multiple myeloma is an incurable disease, with eventual development of drug resistance. Treatments needed to increase progression-free survival or to control the disease with manageable side effects.
- There are variations between professionals on where treatments are placed post 2nd line therapy.
- ISA/POM/DEX expected to be used in current NHS practice as a 3rd or 4th line treatment option.
- No significant different in adverse events expected compared with current treatments in NHS practice.

1.2 **Treatment pathway** (Based on NICE Pathway: Managing myeloma)



1.3 The technology

Mechanism of action	• Humanised monoclonal antibody • Binds to cell surface glycoprotein CD38 • Eventually leads to cell lysis in CD38-expressing tumour cells through triggering antitumor antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, inhibiting enzymatic activity, and apoptosis
Marketing authorisation (for appraisal)	• Expected Q2 2020 • Expected indication: Isatuximab in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy
Existing marketing authorisations	None
Administration and dose	**Isatuximab** • Weight-based dosing • 10 mg/kg intravenous (IV) infusion, weekly for 4 weeks (days 1, 8, 15 and 22), then every 2 weeks **Pomalidomide** • 4 mg orally, on days 1 to 21 of each 28-day cycle **Dexamethasone** • 40 mg (or 20 mg if the patient ≥75 years old) orally or Intravenously, on days 1, 8, 15 and 22 of each 28-day cycle
Cost	• [redacted] (100 mg vial); [redacted] (500 mg vial) • Average cost of course of treatment (ISA/POM/DEX): [redacted] • Isatuximab has an agreed simple discount patient access scheme

1.4 The decision problem

	Final scope issued by NICE	Company submission and ERG comments
Population	Adults with relapsed or refractory multiple myeloma who have received at least 2 or more previous treatments, including lenalidomide and a	• Company: have positioned as a 4th line treatment option, based on discussions with clinicians who state an unmet need at this point in the treatment pathway.

	proteasome inhibitor.	• ERG: population is narrower than the anticipated marketing authorisation and constitutes a post-hoc subgroup of the pivotal clinical trial population (see issue 1).
Intervention	Isatuximab in combination with pomalidomide and dexamethasone (ISA/POM/DEX)	-
Comparator	For people who have had 3 or more prior therapies: • Pomalidomide in combination with dexamethasone (POM/DEX) Note: this is the main comparator in the company's trial • Panobinostat in combination with bortezomib and dexamethasone (PANO/BORT/DEX) Note: although daratumumab therapy offered 4th line in NHS, this is via the cancer drug fund. It is not a comparator because it is not recommended in routine commissioning	• Company: does not consider PANO/BORT/DEX a relevant comparator because rarely used at 4th line in the NHS due to toxicity and perceived lack of effectiveness. • ERG: clinical advisers did not all agree with company's view on PANO/BORT/DEX (see issue 3).
Outcomes	• progression-free survival • overall survival • response rates • duration of response • time to progression • time to next treatment • adverse effects of treatment • health-related quality of life	• Company: also include time-to-discontinuation (TTD) to estimate treatment duration in the model. • ERG: in line with those in the NICE final scope.
Subgroups	None specified	• ERG: company provide subgroup analysis by previous number of treatments.

1.5 Clinical evidence

Table 1: Characteristics of clinical trials

	ICARIA-MM (n=307)	PANORAMA-2 (n=55)
Design	Phase III, randomised, open label, prospective, multi centre, multinational, parallel group, double-arm trial	Single arm phase II trial
Population	Patients who had received **at least 2** prior lines of therapy	Patients who had received **at least 2** prior lines of therapy including an immunomodulatory drug
Intervention	Isatuximab, pomalidomide and dexamethasone (ISA/POM/DEX)	Panobinostat in combination with bortezomib and dexamethasone (PANO/BORT/DEX)
Comparator	Pomalidomide and dexamethasone (POM/DEX)	None
Primary outcomes	Progression-free survival (PFS)*	Overall response rate (ORR)
Secondary outcomes	• Overall response rate (ORR) • Overall survival (OS)* • Time to progression (TTP)* • Treatment-emergent adverse events at grade 3 to 4 and incidence ≥5%*	• Responders to treatment • Time to Response • Progression-free survival • Time to progression • Overall survival
Median follow-up	11.6 months	Not reported

*used in the company model

1.6 Baseline characteristics

Comparison of selected baseline characteristics of ICARIA-MM (intention-to-treat population) and PANORAMA-2 (adapted from CS, Appendix K, Table 42 and ERG report Table 3)

Characteristic		ICARIA-MM		PANORAMA-2
		ISA/POM/DEX (n=154)	POM/DEX (n=153)	PANO/BORT/DEX (n=55)
Median age	Years (range)	68 (36 to 83)	66 (41 to 86)	61(41 to 88)
Gender	Male, n (%)	89 (57.8)	70 (45.8)	29 (52.7)
Eastern Cooperative Oncology Group (ECOG) performance status	ECOG 0, n (%)	55 (35.7)	69 (45.1)	26 (47.3)
	ECOG 1, n (%)	83 (53.9)	68 (44.4)	25 (45.5)
	ECOG 2, n (%)	16 (10.4)	16 (10.5)	4 (7.3)
Median time since diagnosis	Years (range)	4.5 (0.6 to 18.4)	4.1 (0.5 to 20.5)	4.56 (0.6 to 22.0)
MM international staging system (ISS) disease stage n (%)	Stage 1, n (%)	36 (23.4))	41 (26.8)	18 (32.7)
	Stage 2, n (%)	49 (31.8)	48 (31.4)	23 (41.8)
	Stage 3, n (%)	42 (27.3)	44 (28.8))	13 (23.6)
	Unknown, n (%)	27 (17.5)	20 (13.2)	Not reported
	Missing, n (%)	Not reported	Not reported	1 (1.8)
Cytogenetic features n (%)	Absent Del17p, t(4;14) or t(14;16), n (%)	80 (52.3)	80 (52.3)	Not reported
	Present Del17p, t(4;14) or t(14;16), n (%)	33 (21.6)	33 (21.6)	14 (25.5)
	Unknown Del17p, t(4;14) or t(14;16), n (%)	33 (21.6)	33 (21.6)	Not reported
	Present del13q, n (%)	Not reported	Not reported	5 (9.1)
	Present t(11;14)	Not reported	Not reported	14 (25.5)
	FISH normal, n (%)	Not reported	Not reported	2 (3.6)
	FISH showing any abnormality	Not reported	Not reported	35 (63.6)
Number of prior therapies	Median (range)	3 (2 to 11)	3 (2 to 10)	4 (2 to 11)
Prior autologous stem cell transplant	N (%)	83 (53.9)	90 (58.8)	31 (56.4)
Refractory to lenalidomide	N (%)	144 (93.5)	140 (91.5)	Not identified by the ERG

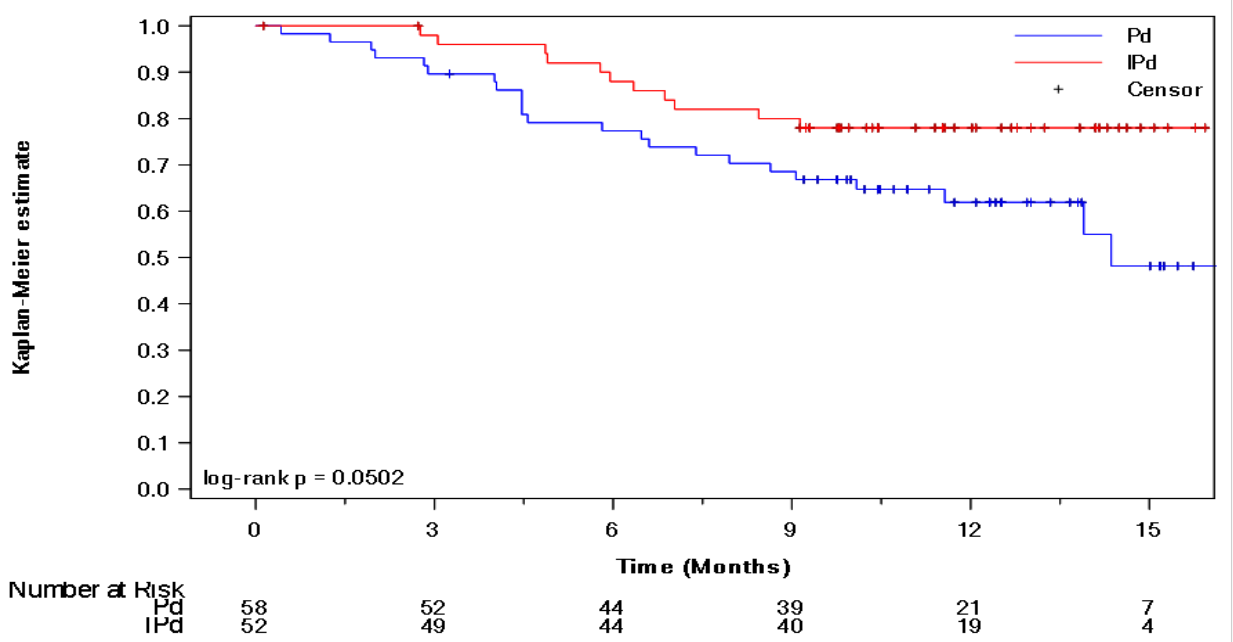
The company compare the baseline characteristics between the ICARIA-MM trial intention to treat population and the ICARIA-MM trial 4th line subgroup (used for the cost-effectiveness results) in tables 8 and 9, pages 41 to 44, of the company submission.

1.7 Key trial results

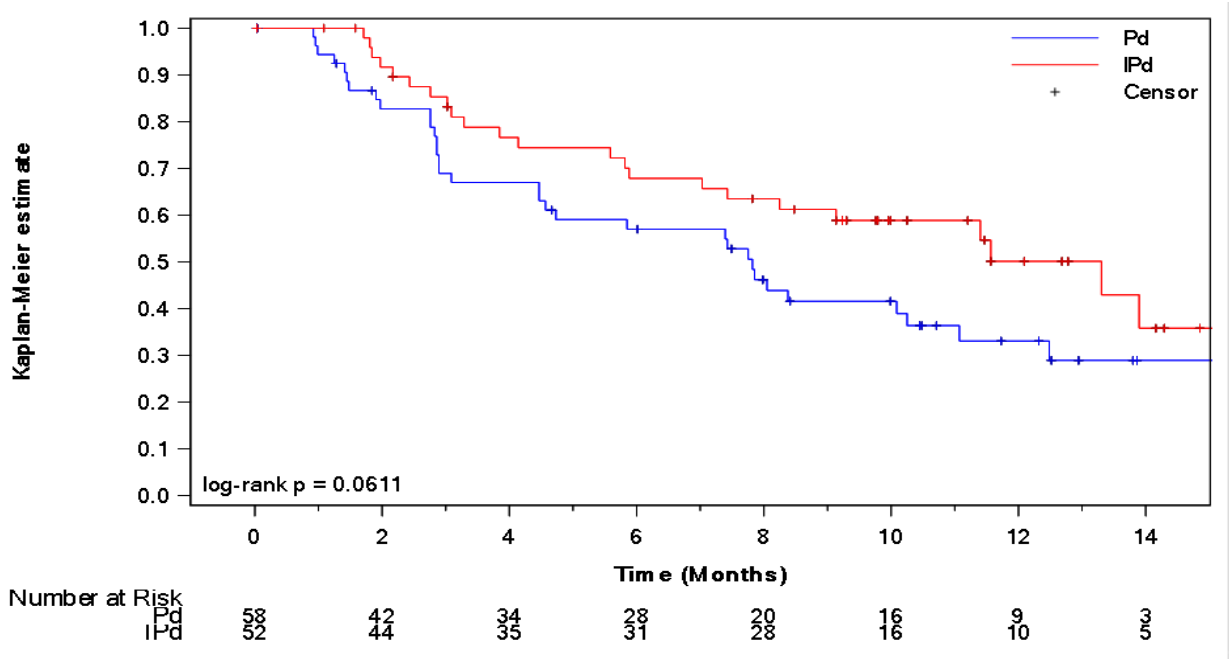
Post hoc analyses in subgroup of patients with 3 prior lines of therapy, n = 58 in POM/DEX arm and n=52 in ISA/POM/DEX arm from ICARIA-MM trial (see issue 1).

ICARIA-MM Trial	**ISA/POM/DEX (n=52)**	**POM/DEX (n=58)**
Median PFS, months (95% CI)	13.3 months, (7.4 to not calculable)	7.82 months (4.5 to 11.1)
Stratified (by age) hazard ratio for PFS for ISA/POM/DEX vs POM/DEX, HR (95% CI) Log-Rank test *p*-value		0.598 (0.348 to 1.030) *p*=0.0611
Median OS, months (95% CI)	Not reached	14.36 (11.6 to not calculable)
Stratified (by age) hazard ratio for OS for ISA/POM/DEX vs POM/DEX, HR (95% CI)		0.49 (0.24 to 1.02) *p*=0.0502
Number of deaths (%)	11 (21.2%)	23 (39.7%)
ORR	53.8%	46.6%
	p=0.3991	

Kaplan Meier Curve for Overall Survival in ICARIA-MM Trial (4th line) (company submission figure 16)



Kaplan Meier Curve for Progression-Free Survival in ICARIA-MM Trial (4th line) (company submission figure 14 page 49).

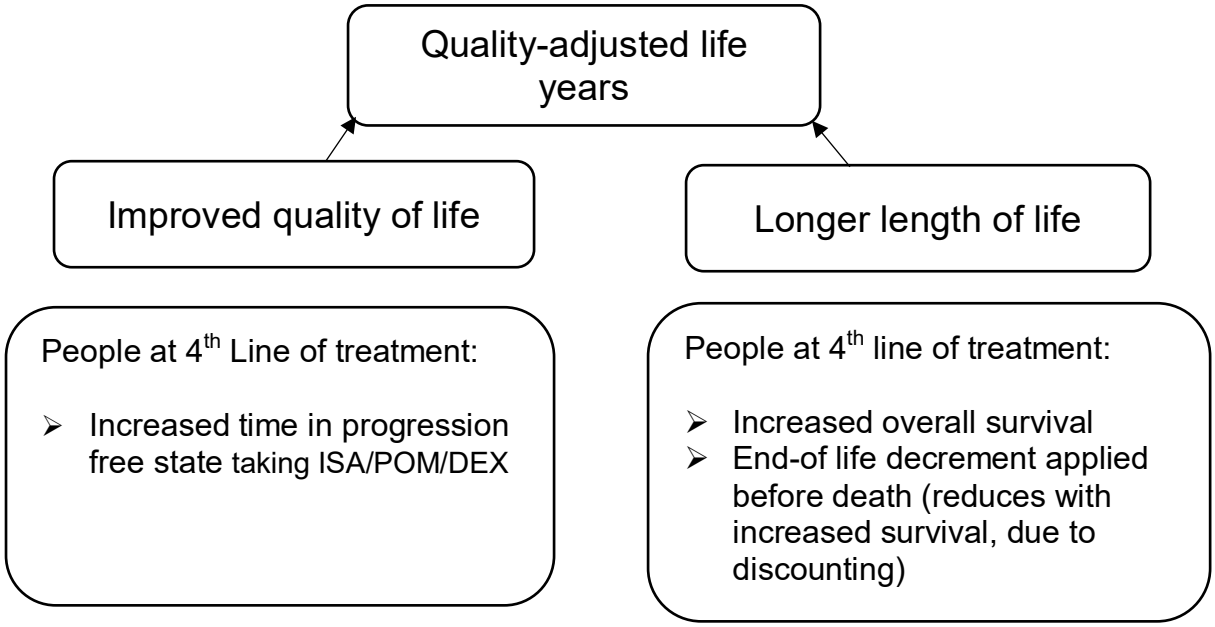


The company also provides clinical results for the intention-to-treat population in Table 11 of the company submission.

The ICARIA-MM clinical trial did not include PANO/BORT/DEX as a comparator. The company compared ISA/POM/DEX with PANO/BORT/DEX using a matching-adjusted indirect comparison (MAIC) including data for ISA/POM/DEX from the ICARIA-MM trial and data for PANO/BORT/DEX from the PANORAMA-2 trial. A MAIC attempts to reduce bias in comparisons of treatment effects between different trial populations by matching baseline characteristics of the trials. The company included various potential or known prognostic factors and/or treatment effect modifiers as covariates in order to reweight the PFS data from the ICARIA-MM ISA/POM/DEX arm to match the distribution of patient characteristics of the PANO/BORT/DEX arm of the PANORMA-2 trial. The company included the following covariates: age, ECOG, gender, presence of one of Del17p, t(4;14) or t(14;16), ISS stage, number of prior treatments, previous stem cell transplant, time since diagnosis and refractory to lenalidomide.

Indirect comparison between ISA/POM/DEX and PANO/BORT/DEX	
Hazard ratio for PFS (95% CI) from MAIC	0.369 (95% CI: 0.259 to 0.526)
Hazard ratio for OS (95% CI) from MAIC	0.642 (95% CI: 0.38 to 1.082)

1.8 Overview of how quality-adjusted life years accrue in the model



Company mapped EQ-5D-3L estimates from EQ-5D-5L (adapted from the company's model)

Health state	Mean utility		
	ISA/POM/DEX	POM/DEX	PANO/BORT/DEX†
Progression-free	0.719	0.717	0.719
Post-progression	0.611	0.611	0.611
End-of life (terminal) decrement	0.225	0.225	0.225

† Underlying utility values for PANO/BORT/DEX were assumed equal to ISA/POM/DEX. However, 0.035 QALYs were deducted in the first cycle to account for differing AE profiles.

1.9 Model structure

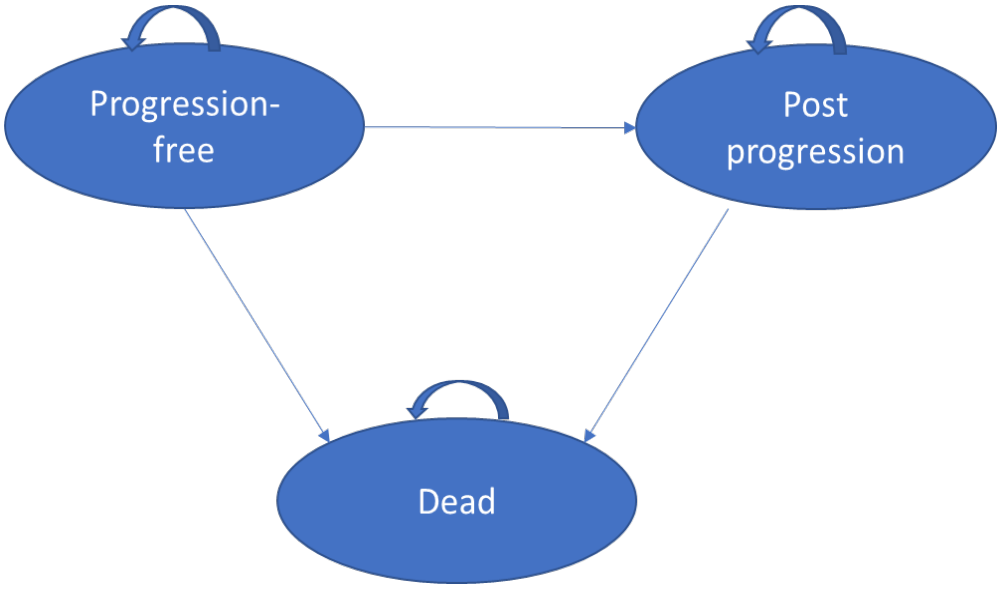
The company constructed a partitioned survival model with 3 health states (progression-free, progressed, and dead). At the clarification stage, the company updated the parameters in its model to model time on treatment independently. This

allows the company to model utility value in the PFS and progressed disease health states separately for people who are on and off treatment.

The probability of being in each model state at time t is estimated for each health state as:

- *Progression Free Survival*: calculated using the PFS survival function (constrained by the OS function and general population mortality) at time t.
- *Post Progression Survival*: calculated as the difference between the cumulative survival probabilities at time t for OS and PFS;
- *Death*: This uses the OS survival function (constrained by general population mortality) at time t.

Model structure



The company derived all clinical inputs for the economic model directly from the ICARIA-MM trial for people who received 3 prior lines of treatments, including lenalidomide for the comparison of ISA/POM/DEX vs POM/DEX. The company used data from the PANORAMA-2 trial using a matched indirect treatment comparison (MAIC) to compare ISA/POM/DEX vs PANO/BORT/DEX. In the company's base

case, a model time horizon of 15 years was applied. The ERG considered that a 20-year time horizon was more appropriate (see issue 7).

1.10 Key model assumptions

The company's base case included:

- Extrapolating OS and TTD: Exponential distribution
- Treatment effect covariate for PFS: A jointly-fitted lognormal model (a model which allows the use of relevant covariates to estimate events) with a treatment effect covariate for PFS
- Acquisition costs of intervention and comparators (drug costs): using TTD survival functions
- HRQoL based on two factors: (i) whether disease has progressed or not, and (ii) which treatment patients received 4th line
- Utility decrement of -0.225 applied for 3 months before death, irrespective of treatment received, to reflect a deterioration in the quality of life in this period, the company calls this a 'terminal decrement'
- Proportion of patients receiving 5th line treatment following ISA/POM/DEX or POM/DEX based on data from ICARIA-MM. The mean duration for each subsequent therapy based on external data (these range from 1 to 9 cycles [each ranging from 1-6 weeks] depending on therapy: *see table 57, company submission*)
- Costs and resource use: Frequency of follow-up and monitoring interventions independent of treatment and progression status
- Costs of subsequent treatments: Ten most frequently prescribed medications in the ICARIA-MM trial at 5th line included
- Costs of terminal care: same irrespective of treatment received
- Adverse events: only if reported in ≥5% of patients in the treatment arms of ICARIA-MM and that were Grade 3 or higher in severity. Probabilities taken from observed data of patients receiving 4th line treatments in ICARIA-MM with costs sourced from NHS Reference Costs 2017/18. Company assumes

disutility of adverse events already captured in the mean utility values from ICARIA-MM data

The company's base case model includes the following additional key assumptions in comparing ISA/POM/DEX with PANO/BORT/DEX:

- HRs obtained from MAIC applied to survival functions for OS and PFS associated with ISA/POM/DEX; the HR obtained for PFS assumed applicable to the survival function for TTD
- HRQoL: Health state utilities and terminal decrement for patients on ISA/POM/DEX also apply to PANO/BORT/DEX
- Adverse events: Probabilities of patients on PANO/BORT/DEX having adverse events, their duration, disutilities, and associated costs based on previous daratumumab NICE Technology Appraisal (TA510), lenalidomide NICE technology appraisal (TA586), and published sources. Probabilities of adverse events assumed applicable to patients on 4th line of treatment for RRMM, even if the original data were not specific to this group of patients
- Proportion of patients receiving each 5L therapy: assumed same regardless of 4th line treatment

More details on key assumptions in the company's model in the ERG report, pages 51 and 52.

2. Summary of the technical report

2.1 In summary, the technical team considered the following:

Issue 1 Company have positioned ISA/POM/DEX as a 4th line treatment, which appears to be supported by clinical expert input. Discussion on other potential treatment pathway positions is absent from the current analyses. The company's analyses at 4th line is based on post hoc analyses. The 4th line subgroup in the clinical trial was not a stratified group and was not randomised, making comparisons between treatments less robust.

Issue 2 Isatuximab is a an anti-CD38 monoclonal antibody. The ICARIA-MM trial excluded people if they had been treated with anti-CD38 monoclonal antibody and were refractory to this treatment. Therefore, the trial provides no clinical evidence for people who have previously taken daratumumab at earlier treatment lines; the Cancer Drug Fund offers daratumumab 2nd line.

Issue 3 The technical team consider PANO/BORT/DEX an appropriate comparator for ISA/POM/DEX. The technical team welcomes comments on when PANO/BORT/DEX would be considered as a treatment option instead of POM/DEX at 4th line.

Issue 4 If PANO/BORT/DEX is an appropriate comparator the matched adjusted indirect comparison (MAIC) used to compare ISA/POM/DEX and PANO/BORT/DEX is exploratory and subject to limitations. It is uncertain if MAIC includes covariates that represent all relevant prognostic factors or treatment effect modifiers. The comparison between ISA/POM/DEX and PANO/BORT/DEX may be biased.

Issue 5 The 5th line treatments used in the clinical trial would not be used routinely in the NHS, for example daratumumab and lenalidomide. The imbalance between the trial arms in the proportion of patients who received subsequent daratumumab or

lenalidomide biases the results on overall survival. Adjustment methods should be considered by the company.

Issue 6 The analyses presented by the company appears to not fully account for the likely level of uncertainty within the modelling of overall survival, progression-free survival and time to treatment discontinuation. This may bias the cost-effectiveness results presented. Consideration should be given to the ERG's sensitivity analysis involving these parameters. Further exploration of appropriate models should be undertaken.

Issue 7 A time horizon of 20 years should be used to capture all relevant benefits and costs that arise as a result of treatment.

Issue 8 Drug acquisition and administration costs may be underestimated for ISA/POM/DEX and correcting this would likely increase the ICER for ISA/POM/DEX. Other cost uncertainties surrounding drug wastage and relative dosing intensities may impact the ICER estimates for ISA/POM/DEX.

Issue 9 There is uncertainty in the health utility values used as they were derived from small sample sizes.

Issue 10 It is unclear whether ISA/PANO/DEX is a suitable candidate for the Cancer Drugs Fund (CDF). ISA/PANO/DEX may not have plausible potential to be cost-effective at the price incorporating the patient access scheme discounts.

Issue 11 Treatment of multiple myeloma in 4th line setting in the absence of ISA/PANO/DEX may meet NICE's end of life criteria, but some uncertainties remain when modelling survival outcomes in the comparator arm.

2.2 The technical team recognised that the following uncertainties would remain in the analyses:

- The ICARIA-MM trial is an open-label trial

- The overall survival data are immature; median overall survival has not been met in the ISA/POM/DEX arm of the ICARIA-MM trial.
- The clinical trial evidence at 4th line is based on small patient numbers (n=110).

2.3 The company's cost-effectiveness results include an agreed commercial arrangement (patient access scheme) for isatuximab.

2.4 Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) that is higher than £50,000 per QALY gained for the comparison between ISA/POM/DEX and POM/DEX, and for the comparison between ISA/POM/DEX and PANO/BORT/DEX when all discounts are included. Commercial arrangements are available for pomalidomide, panobinostat, carfilzomib and lenalidomide and these are confidential so specific ICERs cannot be reported here.

2.5 Based on the modelling assumptions and evidence, the intervention may meet the end-of-life criteria, although there is some uncertainty regarding the modelling outputs in terms of estimated mean survival in the standard care arm of the model (see issue 11). The issue of PANO/BORT/DEX as a relevant comparator should also be taken into consideration (see issue 3).

2.6 The technology is unlikely to be considered innovative (see table 4).

2.7 No equality issues were identified (see table 4).

3. Key issues for consideration

Issue 1 – Treatment pathway and post-hoc subgroup analyses

Questions for engagement	1. Where would ISA/POM/DEX likely be used in NHS clinical practice? Is 4th line the only relevant position for the committee to consider in their decision making? 2. Are the post-hoc subgroup analyses from the ICARIA-MM trial used in the economic modelling robust and appropriate for decision making?
Background/description of issue	**The company** positioned ISA/POM/DEX as a 4th line treatment option for treating relapsed or refractory multiple myeloma. This is a narrower population than both the anticipated marketing authorisation and the ICARIA-MM trial inclusion criteria. The anticipated marketing authorisation requires people to have received 2 prior treatments (including lenalidomide and a proteasome inhibitor) and progressed disease on the last therapy. The ICARIA-MM trial included people who had received at least two prior lines of treatment. The company decided to position ISA/POM/DEX 4th line after receiving clinical expert input which stated unmet need at 4th line. Therefore, the company used a post-hoc analysis of a subgroup of patients in the ICARIA-MM trial in its economic model. **The ERG** notes that the post-hoc analysis involves a group which was not pre-stratified (not a planned subgroup) prior to the start of the clinical trial. This subgroup was not subject to randomisation to eliminate significant baseline differences in prognostic characteristics. They also state, however, that baseline characteristics appear to be similar in both arms of the subgroup analysis in the ICARIA-MM clinical trial. In addition, clinical advice to the ERG stated that because baseline characteristics and clinical characteristics are similar between the 4th line group and the full population in the ICARIA-MM trial, they did not expect the relative efficacy to differ by line of treatment and the post-hoc analyses were considered to be suitable for decision making. The ERG has concerns about the company's 4th line subgroup analyses. They cite issues with the

	company's approach to estimating differential treatment effects in this subgroup and suggest that assessing treatment effects through formal interaction tests is a better approach (ERG report pages 35 to 36). The ERG states that the company should have adjusted for all stratification factors and known prognostic factors simultaneously when estimating the effect of individual covariates. The ERG also had concerns about the company's multivariable regression model and the included variables. The ERG is unclear whether a reduced model would be more appropriate or if interaction terms with the treatment should be included.
Why this issue is important	To appraise ISA/POM/DEX for use within the NHS, the committee must understand the position in the treatment pathway where ISA/POM/DEX is likely to be used. The clinical data underpinning these analyses should be robust and relevant, as this reduces uncertainty associated with the cost-effectiveness results.
Technical team preliminary judgement and rationale	There appears to be a broad consensus from the company, ERG and clinical experts that assessing ISA/POM/DEX as a 4th line treatment is appropriate and reflects the likely position in clinical practice should this treatment be recommended. The technical team are uncertain about the potential use of ISA/POM/DEX at other points in the treatment pathway and welcomes comments on this. The technical team considers that the use of a post-hoc analysis is associated with some uncertainty because of the lack of randomisation and the methods used by the company to adjust for prognostic factors and potential treatment effect modifiers. The technical team has outstanding concerns about the robustness of the post-hoc analysis and would like the company to address the issues raised by the ERG.

Issue 2 – ICARIA-MM clinical trial

Questions for engagement	3. Does using an anti-CD38 monoclonal antibody once have an impact of the effect of using another anti-CD38 monoclonal antibody later in the treatment pathway?
Background/description of issue	Isatuximab is an anti-CD38 monoclonal antibody. The ICARIA-MM trial excluded people previously treated with, and refractory to, an anti-CD38 monoclonal antibody. The population in the NICE scope was not restricted to people who had not previously received and were refractory to an anti-CD38 monoclonal antibody. However, if an anti-CD38 monoclonal antibody has been used once, this could impact the response to using another one.

	The ERG highlights that in clinical practice people at 4th line may have previously taken other anti-CD38 (such as daratumumab, via clinical trials or the Cancer Drugs Fund). The ERG clinical advisers stated that ISA/POM/DEX may be used even in daratumumab-exposed patients in clinical practice provided they were not refractory to daratumumab in a prior line of therapy and had a non-anti-CD38-based treatment in between.
Why this issue is important	It may be appropriate to limit the population to those who have not have an anti-CD38 monoclonal antibody before.
Technical team preliminary judgement and rationale	The technical team are concerned that the patients with prior exposure to an anti-CD38 were excluded from the clinical trials, and that repeatedly using anti-CD38 monoclonal antibodies within a treatment pathway could impact their relative effectiveness. Input from clinical experts about the clinical plausibility would be welcomed. The technical team suggest the population should be focused on those who have either not had an anti-CD38 monoclonal antibody at a prior line of therapy or have had one but were not refractory to it.

Issue 3 – Relevant comparators

Questions for engagement	4. What treatments are considered established clinical practice at 4th line and are therefore relevant comparators for ISA/POM/DEX? 5. Is PANO/BORT/DEX a relevant comparator?
Background/description of issue	The NICE position statement on the consideration of products recommended for use in the Cancer Drugs Fund states that treatments that have been recommended by NICE for use in the Cancer Drugs Fund cannot be considered established practice so should not be included as comparators or in a treatment sequence in the appraisal of a new cancer product. **The company** considers that the only relevant comparator for ISA/POM/DEX at 4th line is POM/DEX as they consider that PANO/BORT/DEX is usually reserved for 5th line use because of its toxicity. The company provided this information from its clinical advisers. The company also state that similar views were documented in previous NICE submissions (TA427, TA510) and market share data

	appears to support the company's view regarding PANO/BORT/DEX as a 5th line treatment. **The ERG** notes a lack of consensus between its clinical advisers regarding 4th line use of PANO/BORT/DEX. One clinical adviser to the ERG stated PANO/BORT/DEX was rarely used due to toxicity and perceived lack of response. However, other clinicians stated PANO/BORT/DEX was used in several regional units with toxicity concerns managed with changes to the dose or schedule. These experts also stated that PANO/BORT/DEX was generally used at 5th line because daratumumab is NICE recommended via the Cancer Drugs Fund (CDF) as a 4th line treatment (TA510). If daratumumab monotherapy was not available, PANO/BORT/DEX would be a treatment option at 4th line along with POM/DEX.
Why this issue is important	To estimate the value of ISA/POM/DEX in the NHS it is important to include the cost and effects of the treatments considered to be established NHS practice in England.
Technical team preliminary judgement and rationale	The technical team note that there is some disparity between clinical expert advice received by the company and the ERG in relation to the positioning of PANO/BORT/DEX in the treatment pathway. The technical team consider that PANO/BORT/DEX is a relevant comparator in this appraisal. PANO/BORT/DEX is recommended as a treatment option by NICE (TA380) at this line of therapy. Some clinical advisers to the ERG state that PANO/BORT/DEX is given, despite its toxicity, to a reasonable proportion of patients in the NHS in England. The technical team would welcome comments when PANO/BORT/DEX may be given instead of POM/DEX, and what factors influences this treatment decision.

Issue 4 – Matched-adjusted indirect comparison

Questions for engagement	6. Is the company's matched adjusted indirect comparison (MAIC) between ISA/POM/DEX and PANO/BORT/DEX valid?
Background/description of issue	ISA/POM/DEX and PANO/BORT/DEX are not part of a connected network of evidence. **The company** compared the two treatments using a matching-adjusted indirect comparison (MAIC) including data from ICARIA-MM and PANORAMA-2 clinical trials. The company included various

	potential or known prognostic factors and/or treatment effect modifiers as covariates in its MAIC to re-weight the PFS data from the ISA/POM/DEX arm in the ICARIA-MM trial to match the distribution of patient characteristics of the PANO/BORT/DEX arm of the PANORAMA-2 trial. The MAIC was used to obtain a hazard ratio for PANO/BORT/DEX compared with ISA/POM/DEX which was applied to the underlying survivor functions used for the ISA/POM/DEX group used in the comparison of ISA/POM/DEX and POM/DEX. The company stated that the MAIC was exploratory and subject to limitations. **The ERG** notes several limitations with the company's approach to comparing ISA/POM/DEX and PANO/BORT/DEX. The ERG states that it is not clear if the covariates the company chose represent all relevant prognostic factors and treatment effect modifiers; if not, the results may be biased. The ERG has concerns with the modelling including the way the treatment effect(s) were defined in the models and mixing baseline estimates from parametric models and estimates of treatment effects from Cox regression. The ERG was also concerned about the use of hazard ratios from a Cox regression model in survival models that are not proportional hazards models. Furthermore, the ERG explains that the results of the MAIC may lack face validity because PANO/BORT/DEX is estimated to have a shorter time to progression than POM/DEX but is estimated to have a longer survival. PFS is typically correlated with OS as death is counted as an event in both metrics. The ERG rated the PANORAMA-2 trial (used to inform the comparison) moderate to poor in terms of trial quality (ERG report table 4), which adds to the uncertainty surrounding the MAIC.
Why this issue is important	There is no direct comparative data for ISA/POM/DEX versus PANO/BORT/DEX. The only available data may not be sufficiently robust to determine the differences between the technologies in how well they work. The ERG state that they are not confident with making inferences from the survival models of ISA/POM/DEX and PANO/BORT/DEX.
Technical team preliminary judgement and rationale	The technical team would like the company to explore and address the ERG's concerns with the MAIC.

Issue 5 – Subsequent treatments

Questions for engagement	7. What treatments are commonly used as a 5th line therapy in NHS clinical practice (not considering current CDF recommended drugs)? 8. Do the subsequent treatments permitted in the ICARIA-MM trial impact on the generalisability of the overall survival data to clinical practice in the NHS?
Background/description of issue	In ICARIA-MM trial numerous treatments were given as subsequent therapies at 5th line and the company include the 10 most commonly used treatments in their economic model. These treatments were bendamustine, bortezomib, carfilzomib, daratumumab, etoposide, thalidomide, lenalidomide, melphalan, panobinostat and pomalidomide. **The company** acknowledge that subsequent daratumumab is unlikely to reflect UK clinical practice and may impact the generalisability of the trial results to the UK. The company report that at data cut-off, 27.6% of the people receiving POM/DEX at 4th line had received daratumumab as subsequent therapy, compared to 3.8% in the ISA/POM/DEX arm. These values increased to 38.1% and 7.1%, respectively, at the July 2019 follow-up. **The ERG** notes that the subsequent use of daratumumab in people who progress at 4th line will potentially be inconsistent with the current clinical management pathway for RRMM in England. Clinical expert advice to the ERG suggests that use of lenalidomide is rare at 5th line in the NHS in England. This may compromise the generalisability of the ICARIA-MM trial results to the context of the NHS in England. The ERG also notes that the imbalance between trial arms in proportion of people receiving daratumumab could have impacted on the effect of ISA/POM/DEX on overall survival. The OS seen in the clinical trial may not be the benefit realised in NHS clinical practice when people are treated with ISA/POM/DEX and POM/DEX, with the estimated OS impacted more in the POM/DEX arm due to the higher proportion receiving subsequent daratumumab in this arm. The costs of 5th line treatments are also incurred in both arms, with the POM/DEX incurring more 5th line treatment costs. The ERG notes that removing the costs of subsequent treatments without adjusting survival would

	be inappropriate. The ERG cannot predict with confidence the impact on the ICER for ISA/POM/DEX if only drugs recommended in England were used in the ICARIA-MM trial. The ERG also notes that time on 5th line treatment in the model was informed from an external source, adding further uncertainty.
Why this issue is important	Treatments received following disease progression in the clinical trial have the potential to influence the relative clinical effectiveness outcomes (specifically survival) for both the intervention and comparator arms in the model. It is important that the key clinical outcome results would reflect those likely to be seen in NHS clinical practice. As 5th line daratumumab was permitted in the clinical trial, but is not NHS clinical practice, this may produce results (both in terms of benefits and costs) that are not likely to be seen in NHS clinical practice. The same applies to the subsequent use of lenalidomide and any other treatments that were given in the trial and would not be in clinical practice.
Technical team preliminary judgement and rationale	The technical team considers that the results of the ICARIA-MM trial may not be generalisable to England due to the use of subsequent treatments in the clinical trial that would not be given in clinical practice. Also, the differential use between trial arms impacts on the OS estimate for ISA/POM/DEX and POM/DEX. This issue also impacts on end of life considerations (see issue 11). The technical team would like to see analyses that attempt to adjust the trial data for treatments which may not be standard NHS practice at 5th line. The team notes that methods to do this include two-stage adjustment analysis, inverse probability of censoring weights and rank preserving structural failure time models. The technical team would like the company to explore each of these methods and adjust the data using the most appropriate approach.

Issue 6 – Extrapolation of overall survival, progression-free survival and time to treatment discontinuation

Questions for engagement	9. How robust is the extrapolation of overall survival, progression-free survival and time to treatment discontinuation? 10. How informative is the ERG's sensitivity analysis regarding the extrapolation of overall survival,

	progression-free survival and time to treatment discontinuation?
Background/description of issue	Clinical data from ICARIA-MM is immature so extrapolation of the data is required to predict long term outcomes. **The company's** preferred base case models were based on the treatment effect diagnostics and test of linearity of Schoenfeld residuals for the proportional hazards assumption, statistical goodness-of-fit, visual comparison with empirical Kaplan-Meier survival functions and the clinical plausibility of the projected survival functions. The models are applied to both treatment arms, and to the comparison of ISA/POM/DEX and PANO/BORT/DEX. Data for the comparison between ISA/POM/DEX and PANO/BORT/DEX comes from the PANORAMA-2 trial for the PANO/BORT/DEX arm, using a MAIC. The company fitted the following models for key clinical events from the observed data form the ICARIA-MM: • An exponential model for overall survival • A jointly fitted lognormal model with a treatment effect covariate for progression-free survival • An exponential model for time to treatment discontinuation (TTD). **The ERG** considers the exponential distribution, as selected by the company, to provide a reasonable representation of the OS data. The exponential survival function for overall survival predicts approximately 10% alive at 10 years, and almost no patients alive at 15 years in the ISA/POM/PD arm. Clinical advice to the ERG suggests that there would be practically no patients alive at 10 years given present treatment options. The ERG considers the jointly fitted lognormal model with a treatment effect covariate to provide a reasonable representation of the PFS data. The ERG believes that the exponential distribution, as selected by the company, appears to provide a good fit to the TTD data. The ERG notes that the company did not report the results of sensitivity analyses using alternative

	functions for overall survival, progression-free survival and time to treatment discontinuation and this underestimates the level of uncertainty in these key parameters. The ERG has selected two distributions which had relatively low BIC values and which have different properties in terms of hazard rates over time to provide an indication of the range of uncertainty within the ICER. The ERG explored the uncertainties in these modelled outcomes in sensitivity analysis by: • Applying a jointly fitted lognormal model and a jointly fitted Weibull model for overall survival • Applying an exponential model and a jointly fitted Weibull model for progression-free survival • Applying a jointly fitted log-logistic model and a jointly fitted Weibull model for overall time to treatment discontinuation.
Why this issue is important	The choice of extrapolation method to model key clinical events affects the estimated clinical and cost-effectiveness results. It is therefore important that any extrapolation method used is valid and robust. Amending the modelling assumptions has the potential to substantially change the ICER estimates, as highlighted by the results from the ERG sensitivity analyses (see tables 1 & 2).
Technical team preliminary judgement and rationale	The technical team considers that the company's choice of models to extrapolate OS, PFS and TTD may be reasonable. The use of other potentially valid models should be explored to capture uncertainties associated with the choice of model as some models displayed similar fit to the data. The technical team would like to see the results reported using a more extensive range of alternative time-to-event models, with discussion on the clinical plausibility of modelled results. The technical team notes that the current ICER estimates are sensitive to the choice of model chosen for key clinical outcomes (see table 1 and 2). The technical team would like the company to provide a plot of empirical hazards and hazard ratios to support the use of an exponential model, which assumes constant treatment effect, for extrapolating OS. The team would also like to see a quantile quantile plot to investigate whether or not the treatment effect (time ratio) for PFS is constant. The implied hazards and treatment effect for each of the alternative time-to-event models should be presented so that the appropriateness of the model can be assessed.

Issue 7 – Time horizon

Questions for engagement	11. Over what time horizon would you expect all differences in benefits and costs that arise as a consequence of treatment choice to materialise?
Background/description of issue	The NICE reference case for economic evaluation notes that the time horizon of an economic model should be "long enough to reflect all important differences in costs or outcomes between the technologies being compared", and as such typically a lifetime horizon is used. However, where extrapolation is uncertain, a longer than required time horizon may exacerbate any over or underestimation in difference of effect over a longer time period. **The company** uses a 15-year time horizon in the model base case analysis. This was assumed to represent a patient's lifetime. At this point 2.5% of modelled patients in the ISA/POM/DEX group are alive, 0.3% in the PANO/BORT/DEX and 0.1% in the POM/DEX group. **The ERG** uses a 20-year time horizon in the ERG base case analysis. At this point, 0.7% of patients were alive in the ISA/POM/DEX group and 0% alive in the POM/DEX and PANO/BORT/DEX groups. The maximum time horizon permitted in the company model is 20 years. The ERG note that the company model does not include additional QALYs accrued by the people who are still alive at 15 years.
Why this issue is important	Having a longer time horizon allows for a greater time for benefits to accrue to balance any costs incurred at the start of the model horizon (for example costs associated with adverse events or treatment which subsequently stops), as well as extenuate the balance between costs and effects of continued treatments.
Technical team preliminary judgement and rationale	The technical team agrees with the ERG that a 20-year time horizon should be sufficient to capture all important benefits and costs arising from choice of treatment.

Issue 8 – Cost uncertainties in the analysis

Questions for engagement	12. Do the differences in the relative dose intensities in the ISA/POM/DEX and POM/DEX arms of the ICARIA-MM trial impact on the robustness of the cost-effectiveness estimates?

	13. Is the assumption of no drug wastage reasonable? 14. Are the costs of treatment underestimated in the company model?
Background/description of issue	There are a number of uncertainties in the analysis associated with costs and resource use. Firstly, there were differences in pomalidomide exposure between the ISA/POM/DEX and POM/DEX arms in the ICARIA-MM trial. The mean relative dose intensity (RDI) of pomalidomide was [redacted] (Standard deviation: [redacted]) in the ISA/POM/DEX arm, and [redacted]% (Standard deviation: [redacted]) in the POM/DEX arm. This may have resulted from the open-label nature of the trial (see table 3). **The ERG** investigated the impact of assuming 100% relative dose intensity for all 4th line drugs on cost-effectiveness results (see table 1 and 2). The ERG acknowledges that the sensitivity analysis of assuming that all reductions in dose intensities were not pre-planned and were associated with drug wastage is an extreme scenario. However, the ERG believes that these scenario analyses are informative. **The company** stated that all medication is dosed by milligrams (mg), and there was a possibility of using fractions of vials which may result in no drug wastage (see table 1 and 2). **The ERG** and company undertook scenario analysis to investigate the effect of assuming no drug wastage. In addition, the ERG believes the company had potentially inaccurately estimated drug acquisition and administration costs. This is due to the cycle length of the model (1 week) being shorter than the frequency at which treatments are provided in clinical practice. They note that isatuximab is given fortnightly after the first 4 weeks. They explain that drugs costs are underestimated by patients discontinuing in the week that treatment is provided with the next week's costs not being accounted for. The ERG expects that amending this assumption would increase the ICERs of ISA/POM/DEX compared with both POM/DEX and PANO/BORT/DEX.
Why this issue is important	To have confidence in reported cost-effectiveness results, analysis should attempt to capture the likely costs that would be incurred in NHS clinical practice for each potential treatment option.
Technical team preliminary	The ERG's scenario analysis is useful as it attempts to account for some areas of cost uncertainty

judgement and rationale	within the analyses (see table 3 and 4). The potential underestimation of drugs costs due to the cycle length of the model and the dosing schedule for isatuximab should be investigated and amended by the company to provide more accurate cost-effectiveness estimates. The technical team believes that the assumption of zero drug wastage to be an extreme and unlikely scenario. The team also considers that the difference in relative dosing intensities may result in cost estimates that are not reflective of those in clinical practice and likely result from the open-label nature of the ICARIA-MM trial. The technical team would like to receive comments on the likely impact of key cost uncertainties outlined in the evidence base for ISA/POM/DEX.

Issue 9 – Health utility values

Questions for engagement	15. Are the utility values included in the company model appropriate?
Background/description of issue	HRQoL was assessed using the EQ-5D-5L health state utility index (mapped to EQ-5D-3L values) and visual analogue scale was similar between groups and worsened slightly over time, although slightly more so in the ISA/POM/DEX arm than the POM/DEX arm. EQ-5D-5L data were collected in the ICARIA-MM trial on day 1 of each treatment cycle (every 2 weeks) and 60 days (±5 days) after last study treatment administration. The company urge caution in interpreting these results due to a small sample size in the 4th line population and absence of significance testing. The utility values used in the analyses is 0.719 and 0.717 for progression-free health state for the ISA/POM/DEX and POM/DEX respectively. A value of 0.611 is used for the progressed disease state with an end of life decrement of 0.225 applied in the final 4 weeks of life. The same health utility values by health state are assumed for the PANO/BORT/DEX arm as the ISA/POM/DEX arm.
Why this issue is important	To have confidence in reported cost-effectiveness results, the health utility values used should be valid. Changes in health utility values have the potential to change the ICER estimate, as they can change the estimated QALY gains between treatment options.
Technical team preliminary judgement and rationale	The technical team consider that the clinical data from ICARIA-MM is immature, which adds uncertainty to the health utility results. The team recognise that one of the strengths of the analysis

	is that health utility values are directly collected from the ICARIA-MM trial.

Issue 10 – Cancer Drugs Fund

Questions for engagement	15. Is there further data being collected that could reduce uncertainty surrounding longer-term effectiveness and health outcomes in the relevant population(s)? 16. When will these additional data become available? 17. How suitable is the technology for use in the Cancer Drugs Fund (CDF)?
Background/description of issue	The median follow-up at the interim analysis cut point is 11.6 months, meaning that the clinical data is immature. This increases the uncertainty associated with the results from the model. The ICARIA-MM trial is ongoing with future data collection planned. Final OS analyses are planned once 220 deaths have been observed (anticipated Q2 2021). This is for the ITT population and not the 4th line subgroup.
Why this issue is important	The CDF is a potential option if there is plausible potential for the drug to satisfy the criteria for routine commissioning, but there is significant remaining clinical uncertainty which needs more investigation, through data collection in the NHS or clinical studies. This means the CDF will fund the drug, to avoid delaying patient access, but would require further information on its effectiveness before it can be considered for routine commissioning when the guidance is reviewed.
Technical team preliminary judgement and rationale	The technical team note that the current clinical trial data is very immature and that further data collection is planned and this may reduce important uncertainties in clinical outcome data. However, the technical team also notes that there are clinical uncertainties that remain in any further data collection, such as the use of subsequent treatments which are not used (or used rarely) within the NHS at 5th line (see issue 4) and the open-label nature of the trial. Therefore, the technical team is unclear if ISA/POM/DEX is a suitable candidate for the cancer drugs fund.

Issue 11 – End of Life

Questions for engagement	18. Under standard care, is the life expectancy of adults with relapsed or refractory multiple myeloma after 3 prior treatments less than 24 months?

	19. Does ISA/POM/DEX extend life for more than 3 months compared with standard care for adults with relapsed or refractory multiple myeloma after 3 prior treatments?
Background/description of issue	NICE states that for technologies to be considered against its end of life criteria if it meets certain conditions, namely; • The treatment is indicated for patients with a short life expectancy, normally less than 24 months and; • There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment. **The company** notes that patients with multiple myeloma at 4th line treatment and beyond have a median OS of 5.1 months (data from Usmani et al). The technical team recognise that the mean value would be longer than the median. The company also cites previous NICE technology appraisals in multiple myeloma, TA427 (pomalidomide) and TA510 (daratumumab), which both considered a 4th line population. In both appraisals the committee concluded that the short life expectancy criterion had been met. The company also state that median survival estimates from the model are less than 2 years in the comparator arm. The company also note that the overall survival in the control arm should be interpreted with caution due to high levels of censoring (incomplete information) and use of subsequent therapy, in particular daratumumab (see issue 4). **The ERG** notes the company's model predicted that the probabilistic and deterministic estimate for mean survival for those on POM/DEX was [redacted] years and [redacted] years, respectively. For patients receiving PANO/BORT/DEX (estimated using the MAIC), these values were [redacted] and [redacted] years. Therefore, the ERG considers that it is uncertain if the short life expectancy criterion is met. The ERG also state that the company's model predicts that ISA/POM/DEX will increase life expectancy by 1.628 years compared with POM/DEX and by 1.056 years compared with PANO/BORT/DEX, although the gain compared with PANO/BORT/DEX is uncertain due to the comparison being informed by the MAIC. Given these values, the ERG agrees that it is likely that the criterion for extension to life is met.

Why this issue is important	A technology which meets the NICE end of life criteria has an increased maximum acceptable ICER.
Technical team preliminary judgement and rationale	The technical team considers that the life expectancy of people receiving standard care may be less than 24 months, based on previous NICE technology appraisals in this disease area and on the evidence presented by the company. However, the mean survival estimates from the company model may not support this. The technical team considers that there is sufficient evidence to indicate that the treatment offers an extension to life of at least an additional 3 months, compared to both POM/DEX and PANO/BORT/DEX, and therefore ISA/POM/DEX meets the extension to life criteria. Therefore, the technical team consider that ISA/POM/DEX may meet the end-of-life criteria for this indication, although there is some uncertainty regarding the modelling outputs in terms of estimated mean survival in the standard care arm of the model. The issue of PANO/BORT/DEX as a relevant comparator should also be taken into consideration (see issue 3 and 4) along with the issue of subsequent use of daratumumab and differential daratumumab (and lenalidomide) use between the trial arms (see issue 5) when deciding whether ISA/POM/DEX meets NICE's end of life criteria for this indication. In addition to this, the choice of models used in the ERG sensitivity analysis to extrapolate OS in the models may also impact the estimated life expectancy (see issue 6).

4. Issues for information

Tables 1 to 4 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate for the comparison between ISA/POM/DEX versus POM/DEX (ICERs and change from company base case do not include confidential PAS discounts which are available for pomalidomide, panobinostat, lenalidomide and carfilzomib so are only illustrative)

Alteration	Technical team rationale	ICER – deterministic (PSA)	Change from company base case (PSA)
Company base case	**-**	**£118,816**	**-**
1. ERG correction of minor errors in the company's economic model	Technical team agree with ERG's correction of modelling errors	£126,611	**+£7,795**
2. Extending the time horizon from 15 to 20 years (see issue 7)	Technical team agree with ERG that a 20-year time horizon captures all relevant benefits and costs	£115,996	**-£2,280**
3. Combining ERG amendments 1 & 2 as above (ERG base case*)	Technical team agree with both amendments	£123,769 (£133,461)	**+£4,953 (+£14,645)**
Scenarios 1 and 2 are also applied in each of the scenarios 4a to 8			
4a. Use of a jointly fitted lognormal model for OS	Technical team considers the ERG's sensitivity analyses surrounding the extrapolations of OS, PFS and TTD to be appropriate	£123,041	**+£4,225**
4b. Use of a jointly fitted Weibull model for OS	As above.	£176,028	**+£57,212**

Alteration	Technical team rationale	ICER – deterministic (PSA)	Change from company base case (PSA)
5a. Use of an exponential model for PFS	As above	£124,987	**+£6,171**
5b. Use of a jointly fitted Weibull model for PFS	As above	£126,281	**+£7,465**
6a. Use of a jointly log-logistic model for TTD	As above. The technical team notes that using a jointly fitted log-logistic model for TTD substantially increases the ICER	£213,105	**+£94,289**
6b. Use of a jointly fitted Weibull model for TTD	As above	£127,115	**+£8,299**
7. No wastage considered	The technical team note that assuming no drug wastage may be optimistic – but considers this ERG sensitivity analysis informative	£103,095	**-£15,721**
8. Setting all relative dose intensities to 100%	The technical team note that assuming no drug wastage may be extreme – but considers this ERG sensitivity analysis informative	£134,932	**+£16,116**
***Technical team's preferred assumptions: ERG base case (which combines alterations 1 & 2).** (The technical team note that the ERG's sensitivity analysis, particularly around the use of different models for OS, PFS and TTD – Alterations 4a to 6b, should also be considered in decision-	**–**	£123,769 (£133,461)	**+£4,953 (+£14,645)**

Alteration	Technical team rationale	ICER – deterministic (PSA)	Change from company base case (PSA)
making)			

Table 2: Technical team preferred assumptions and impact on the cost-effectiveness estimate for the comparison between ISA/POM/DEX versus PANO/BORT/DEX (see issue 3) (ICERs and change from company base case do not include confidential PAS discounts which are available for pomalidomide, panobinostat, lenalidomide and carfilzomib so are only illustrative)

Alteration	Technical team rationale	ICER – deterministic (PSA)	Change from company base case (PSA)
Company base case	**-**	**£216,856**	**-**
1. ERG correction of minor errors in the company's economic model	Technical team agree with ERG's correction of modelling errors	£215,793	**-£1,063**
2. Extending the time horizon from 15 to 20 years (see issue 6)	Technical team agreed with ERG that a 20-year time horizon captures relevant benefits and costs	£210,812	**-£6,044**
3. Combining ERG amendments 1 & 2 as above (*ERG base case)	Technical team agree with both amendments	£210,102 (£238,300)	**-£6,754 (+£21,444)**
Scenarios 1 and 2 are also applied in each of the scenarios 4a to 8			
4a. Use of a jointly fitted lognormal model for OS	Technical team considers the ERG's sensitivity analyses	£165,233	**-£51,623**

Alteration	Technical team rationale	ICER – deterministic (PSA)	Change from company base case (PSA)
	surrounding the extrapolations of OS, PFS and TTD to be appropriate		
4b. Use of a jointly fitted Weibull model for OS	As above	£289,568	**+£72,712**
5a. Use of an exponential model for PFS	As above	£215,967	**-£889**
5b. Use of a jointly fitted Weibull model for PFS	As above	£220,920	**+£4,064**
6a. Use of a jointly fitted log-logistic model for TTD	As above	£365,613	**+£148,757**
6b. Use of a jointly fitted Weibull model for TTD	As above	£216,046	**-£810**
7. No wastage considered	The technical team note that assuming no drug wastage may be optimistic – but considers this ERG sensitivity analysis informative	£191,148	**-£25,708**
8. Setting all relative dose intensities to 100%	The technical team note that assuming no drug wastage may be extreme – but considers this ERG sensitivity analysis informative	£224,136	**+£7,280**
***Technical team's preferred assumptions: ERG base case (which combines alterations 1 & 2).** (The technical team note that the ERG's sensitivity analysis, particularly around the use of	–	£210,102 (£238,300)	**-£6,754 (+£21,444)**

Alteration	Technical team rationale	ICER – deterministic (PSA)	Change from company base case (PSA)
different models for OS, PFS and TTD – alterations 4a to 6b, should also be considered in decision-making)			
**The ERG notes that if a full incremental analysis was considered appropriate, PANO/BORT/DEX dominates POM/DEX and the ICER for ISA/POM/DEX would be that compared with PANO/BORT/DEX. However, the limitations of the MAIC need to be considered when evaluating the comparison of ISA/POM/DEX and PANO/BORT/DEX (see issue 4).			

Table 3: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
ICARIA-MM is an open-label trial	The ICARIA -MM trial is an open-label trial, meaning that trial participants know the treatment they are receiving. This has the potential to introduce bias results which may have been influenced by which treatment arm participants were assigned to.	The ERG considers that the open-label nature of the ICARIA-MM clinical trial may have impacted on measurements taken and on patients' self-administration of pomalidomide and note that for oral pomalidomide, the relative dose intensity was higher in the POM/DEX arm than in the ISA/POM/DEX arm. They state that the impact of the trial design is difficult to assess.
Small patient numbers	The ICARIA-MM trial included 110 patients receiving treatment at 4th line (52 people receiving ISA/POM/DEX and 58 receiving POM/DEX)	Unknown

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
ICARIA-MM is an open-label trial	The ICARIA -MM trial is an open-label trial, meaning that trial participants know the treatment they are receiving. This has the potential to introduce bias results which may have been influenced by which treatment arm participants were assigned to.	The ERG considers that the open-label nature of the ICARIA-MM clinical trial may have impacted on measurements taken and on patients' self-administration of pomalidomide and note that for oral pomalidomide, the relative dose intensity was higher in the POM/DEX arm than in the ISA/POM/DEX arm. They state that the impact of the trial design is difficult to assess.
	The effectiveness estimates are therefore highly uncertain as there is less evidence to inform appropriate extrapolation methods.	
Immature evidence base	The median follow-up in the 4th line subgroup from the ICARIA-MM trial was only 11.6 months. With an immature data set, there is less evidence to inform appropriate extrapolation methods on key clinical outcomes.	Unknown. Limited data informing key outcomes adds uncertainty to the cost-effectiveness results.

Table 4: Other issues for information

Issue	Comments

Errors in company model	The ERG identified two model errors. The first was that the QALY decrement associated with reduced HRQoL at the end of life is applied incorrectly as the negative value is subtracted rather than added to overall QALYs. The second error was that the company did not incorporate the weighting of dexamethasone by oral and intravenous administration when calculating the average administration costs. Correcting this reduces the costs associated with POM/DEX but has no impact on the costs of ISA/POM/DEX as only the highest administration cost was assumed. ERG corrects both of these errors in their base case (see tables 1 & 2 in Section 4).
Underestimation of uncertainty in the decision problem	The ERG notes that there is outstanding uncertainty in the economic model concerning the inputs and modelling of adverse event data. The ERG suggests that resolving this would result in a small increase in the probabilistic ICER due to the increased uncertainty. The ERG cannot predict this with certainty.
Potential face validity violations in the utilities sampled within the PSA	The ERG notes that in probabilistic sensitivity analysis it was possible that sampled mean utility for patients in progressed disease could be higher than that for patients in progression free state, which the ERG does not believe to be plausible. The ERG does not anticipate that removing this limitation would markedly change the central ICER estimate but notes that the current sampling methodology is likely to increase the uncertainty within the PSA.
Innovation	The company considers ISA/POM/DEX to be innovative. However, the technical team considers that all relevant benefits associated with the drug are adequately captured in the model and the QALY calculation.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.
Patient characteristics in the ICARIA-MM study	Clinical advice received by the ERG suggested that the patient characteristics of the ICARIA-MM trial (including the ITT and 4L populations) are broadly reflective of clinical practice in England, albeit being slightly younger and with a slightly lower proportion of black patients. The difference in the average age between patients in the ICARIA-MM trial and in England may result in a different treatment effect, although the ERG is unable to comment on whether this would be less or greater for patients in England compared with that estimated in the trial. Clinical advisers to the ERG believed that the lower proportion of black patients would not affect the estimate of treatment efficacy.
Inconsistency in the proportion of people	The ERG identified a discrepancy. The ERG were concerned that the model may have used

receiving daratumumab at 5L reported in the CS and used in the model	data for subsequent therapies from a later cut point than other outcomes such as OS. The ERG has assumed that the values in the model are correct and comments that it is unlikely that the use of alternative figures would reduce the company's base case below £50,000 per QALY.
Company assumptions	The company assume the proportion of ISA/POM/DEX patients receiving granulocyte-colony stimulating factor and red blood cell and platelet transfusions were assumed to be the same as that for POM/DEX. The company also state that a number of cost estimates were based on assumptions which may add more uncertainty to the model. These were not explored further by the ERG.

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Technical engagement response form

Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [ID1477]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **Thursday 9 April 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise,

all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Sanofi UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**n/a**

Key points: Updated base case

As highlighted during the technical engagement stage, we have updated our model to reflect (a) all model edits suggested by the ERG and (b) an increased PAS discount (***academic/commercial in confidence information removed***) for isatuximab in order to meet the requirements of the WTP threshold for end of life medicines and entry into the Cancer Drugs Fund (CDF). All responses to the issues raised in the Tech report relate to this updated model. A change log of all updates made to the model is submitted with this response.
Below is a summary of the updated ICER including the updated ***academic/commercial in confidence information removed*** discount for isatuximab and with pomalidomide at list price.

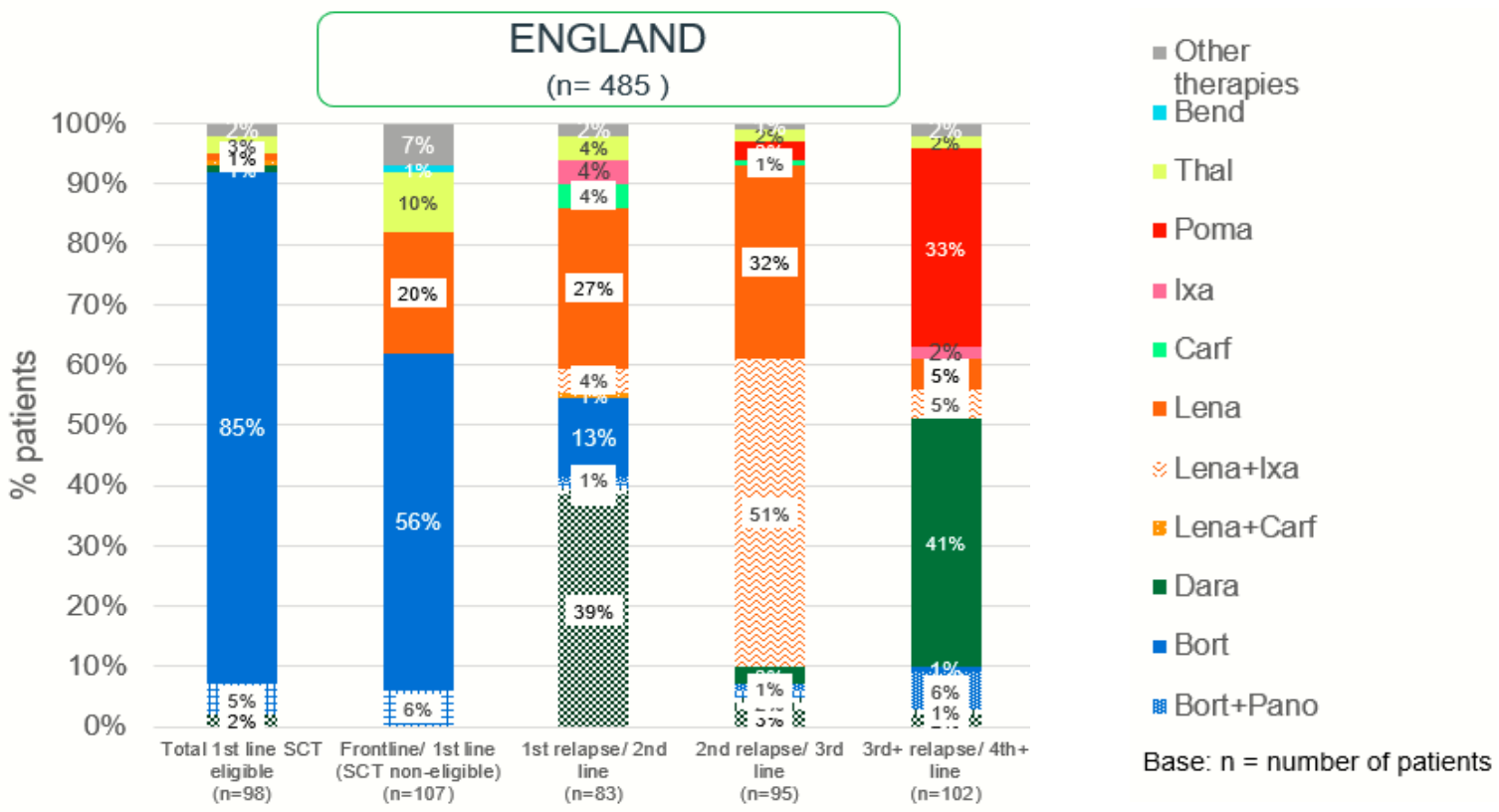
	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	ICER (deterministic) (£/QALY)
Sanofi updated base case (OS & TTD: Exponential; PFS: Lognormal (R))							
IsaPd	***Academic/commercial in confidence information removed***			1.689	1.102	113,179	**102, 725**
Pd				-	-	-	**-**

Academic/commercial in confidence information removed

Questions for engagement

Issue 1: Treatment pathway and post-hoc subgroup analyses	
1. Where would ISA/POM/DEX likely be used in NHS	On 26th March 2020, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for isatuximab (Sarclisa®) in combination with pomalidomide and dexamethasone (IsaPd) intended for the treatment of multiple myeloma (1). The indication is for:

clinical practice? Is 4th line the only relevant position for the committee to consider in their decision making?	*'Isatuximab, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) and have demonstrated disease progression on the last therapy.'* (Please note that with the approved label now available, the indicated population is relapsed **and** refractory multiple myeloma and this should be reflected in the final NICE recommendation for isatuximab. Therefore, we request that all NICE documents relating to this appraisal are updated to reflect the CMHP approved indication). At present in the UK multiple myeloma pathway, this indication means IsaPd could be used at third line (3L) or later. However, the anticipated place in therapy for IsaPd in England and Wales is at 4L which represents a sub-population of the full licence. These are patients who have received 3 prior lines of treatment, including lenalidomide and a PI. This is based on the following reasons: • According to clinical expert opinion solicited during a Sanofi advisory board carried out in March 2019, IsaPd would likely be used at 4L as there remains high unmet need for these patients who have failed lenalidomide or are double refractory to lenalidomide and a PI (2). • Pd, the comparator in ICARIA-MM, is recommended by NICE at 4L, therefore the natural place for IsaPd is 4L where it is expected to displace Pd. • To be eligible for IsaPd treatment in the ICARIA-MM trial, patients must have already received lenalidomide and a PI treatment (which is reflected in the licence). Recently, lenalidomide has been recommended by NICE at first line (1L) for transplant ineligible patients if thalidomide is not appropriate; it is also available at second line (2L) in patients who have received bortezomib (3,4). However, these are new changes to the pathway in England/Wales and according to market research data obtained by Sanofi during 2019 Oct/No (n=95 patients), lenalidomide remains to be generally used at 3L (32%) via routine commissioning with dexamethasone and 51% in combination with ixazomib (via CDF) (Figure 1) making the 4L position for isatuximab most appropriate (5). • IsaPd was granted a positive scientific opinion by the MHRA for an Early Access to Medicines Scheme (EAMS) based on the high unmet medical need at 4th line in the UK on 02/12/2019 (6). The rapid uptake onto the scheme highlights the need for triplet antibody therapy at 4L. Sanofi did consider other positions in the treatment pathway. The clinical and cost-effectiveness analysis for IsaPd in other lines

	(3L, 4L+) have been reported in the company submission in scenario analyses. In light of the above arguments, and the cost-effectiveness challenges for combination branded medicines, the 4L position represents the most appropriate use of IsaPd for patients within the NHS based on the clinical evidence and was therefore chosen for the base case. **Figure 1: IQVIA Multiple myeloma therapy monitor, UK report (Oct/Nov, 2019) – Regimen share at lines of therapy in England** 
2. Are the post-hoc subgroup analyses	We have performed a number of analyses to support the robustness of the data used in the model for the 4L population. These

from the ICARIA-MM trial used in the economic modelling robust and appropriate for decision making?	include statistical tests to understand the consistency of effect in the ITT and 4L population for PFS, assessment of confounding factors and evaluation of interaction effects of subgroups. **ITT** Multi-variate/multi-variable (MV) analyses with stratification for age in the ITT population has been performed with a full model (all prognostic factors included), reduced model (only factors considered statistically significant) and clinically relevant model (factors considered statistically significant plus additional factors considered prognostic by Sanofi clinical expert). The HR for IsaPd vs Pd with respect to PFS is consistent across all three models: HR for full model is ***academic/commercial in confidence information removed***, reduced model is ***academic/commercial in confidence information removed*** and the clinical model is ***academic/commercial in confidence information removed*** suggesting consistent effect. **4L** Descriptive statistic tests were used to compare the baseline characteristics of the 4L population using Fischer exact test and Kruskal-Wallis test. The results suggest that there are no differences and two arms are reasonably balanced in terms of baseline demographics. Interaction tests were also performed on the subgroups in 4L population using Cox proportional hazard including age (<75 years versus ≥75 years), the factor, treatment effect and the treatment by factor interaction for age, baseline/demographic characteristics, disease characteristics, cytogenetics at entry, prior myeloma treatment (i.e. prior PI and prior lenalidomide). The p-value are all non-significant suggesting that there is no significant difference across categories of the subgroups. MV analysis with stratification for age in the 4L population has also been performed with a full model (all prognostic factors included), reduced model (only factors considered statistically significant) and clinically relevant model (factors considered statistically significant plus additional factors considered prognostic by Sanofi clinical expert). The HR for IsaPd vs Pd with respect to PFS for each model is: HR for full model is ***academic/commercial in confidence information removed*** (full model using same variables, except number of prior lines, as used in the ITT model). A second full model was conducted to see if there is a difference in adapting the factor to our population, so the factor REGION (geographical) was dropped (there are too many categories for our sample size and there is already another REGION factor (regulatory) with less categories) and there is

	very few patients in Other and Asian categories of the RACE (and no event), so these two categories were pooled. The HR is in this 2nd full model is ***academic/commercial in confidence information removed***. The reduced model is ***academic/commercial in confidence information removed*** and the clinical model is ***academic/commercial in confidence information removed***, again suggesting consistent effect. Detailed results for this are provided in a confidential reference accompanying this response (7).
Issue 2: ICARIA-MM clinical trial	
3. Does using an anti-CD38 monoclonal antibody once have an impact of the effect of using another anti-CD38 monoclonal antibody later in the treatment pathway?	The ICARIA-MM trial excluded patients who were refractory to daratumumab/prior anti-CD38 only. Patients who had received anti-CD38 treatment and were not refractory were permitted entry into the trial (8). However, given the timing of study, it is likely that there were very few patients with prior anti-CD38 treatment history available for enrolment in the study. As a result, one patient entered the trial having received prior anti-CD38 therapy. Sanofi accept that the availability of daratumumab in combination with bortezomib and dexamethasone (DVd) at 2L via CDF means there will be a diminishing number of patients at 4L over time who may be eligible for isatuximab treatment (9). This assumes that a restriction on retreatment with an anti-CD38 after prior exposure is in place. However, we request that the appraisal committee considers this retreatment issue carefully in their deliberations from a clinical and patient perspective. Although there is no information to date on re-treatment/sequencing of anti-CD38 monoclonal antibodies and impacts on response, we provide some information below which may help to inform this discussion and suggest that this is validated with clinical experts. In an advisory board held by Sanofi in March 2019, clinical experts believed that there was a strong scientific rationale for anti-CD38 retreatment at 4L for the following reasons (2): • Isatuximab and daratumumab are different anti-CD38 mAbs. This is because they bind to different specific epitopes on the human cell surface antigen CD38 • The combination of an anti-CD38 mAb with an immunomodulatory agent (IMiD) (for example, isatuximab in combination with pomalidomide, an IMiD) is considered more effective than with a PI (for example, daratumumab is currently used at 2L in combination with bortezomib, a PI) • Pomalidomide could be a superior IMiD to lenalidomide

	Similar views regarding retreatment with anti-CD38 mAbs have been captured in other market research conducted by Sanofi, particularly if: 1) the patient has not become refractory to a prior anti-CD38 mAb or 2) where a line of treatment has been skipped (10,11). There is limited evidence emerging regarding CD38 expression recovering after 6 months (12,13). Indeed, the experts who informed the ERG report agreed that re-treatment under these circumstances could be a reasonable clinical decision. Therefore, it would appear there is clinical support for re-treatment in the appropriate patient, despite the lack of formal evidence. This is a clinical question that could be addressed via the CDF since anti-CD38 retreatment is a key issue given the positioning of DVd at 2L.
Issue 3: Relevant comparators	
4. What treatments are considered established clinical practice at 4th line and are therefore relevant comparators for ISA/POM/DEX?	From the latest Sanofi market research data for 4L+ RRMM (Figure 1), the main comparator is Pd**,** making up 33% of market share. Daratumumab is used in a larger proportion of patients, and it is anticipated that IsaPd will displace daratumumab at 4L, but as a CDF treatment, it is not considered a relevant comparator. Panobinostat in combination with bortezomib and dexamethasone (PanVd) makes up 6% of current market share (5). This distribution of main treatment options are in line with clinical expert opinion obtained by various sources. Clinical experts consulted during advisory boards or expert elicitation meetings have consistently indicated limited use of the PanVd combination at 4L due to its associated toxicities (2,14). In clinical practice, clinicians have told us that PanVd is reserved for later lines (e.g. fifth line (5L)) where patients are expected to have limited capacity to benefit to the extent suggested by PFS and OS data from the panobinostat study, PANORAMA-2 (14). PanVd has been listed by NICE as comparator in other 4L appraisals, but clinical experts who contributed to these appraisals have expressed similar views meaning that reserving PanVd for later lines has been established practice for some time (TA427 and TA510) (15,16). The ERG report that two of the three clinical experts consulted by them suggested that PanVd would be used at 4L in the absence of daratumumab monotherapy. These experts also said that because of daratumumab use at 4L, PanVd would be used in later lines implying that if daratumumab were not available then PanVd would be used at 4L. However, market research data over time has demonstrated that PanVd usage has remained low and relatively unchanged. The IQVIA multiple myeloma therapy monitor UK report for Oct/Nov, 2019 (Figure 1) for therapies used at 4L and later (4L+) indicate current Daratumumab use in 41% of patients, Pd at 33% while PanVd is 6% (5). Whilst we do not have access to data specifically for

5L it is worth noting that the data presented here includes 4L+ and the PanVd data in particular will reflect usage beyond 4L. (Daratumumab and pomalidomide are not typically used beyond 4L in the UK).

The IPSOS myeloma 4L+ regimen share over time data, shown below in Table 1. These data are derived from individual patient records from a sample of physicians and used to project annual market share data for 4L+ patients in the UK. The data indicates that in 2017 before daratumumab became available on the CDF, PanVd had low (7%) market share despite the fact that daratumumab was not available at that time (17). Moreover, it was not considered a relevant comparator during the daratumumab monotherapy appraisal (TA510). Since then PanVd has declined to 1% in the 4L+ setting. This would suggest that PanVd is hardly used and if so, is likely to be reserved for later lines irrespective of availability of daratumumab at 4L.

Table 1: IPSOS – Myeloma 4L+ Regimen share for daratumumab, pomalidomide (with dexamethasone) and Panobinostat (with bortezomib and dexamethasone)

Regimen	Time period		
	Jan 2017 - Dec 2017[a]	Jan 2018 - Dec 2018[b]	Jan 2019 - Dec 2019[c]
Daratumumab	1%	21%	39%
Dexamethasone/ Pomalidomide	74%	31%	18%
Daratumumab/ Dexamethasone	-	1%	10%
Bortezomib/ Daratumumab	-	-	2%
Bortezomib/ Daratumumab/ Dexamethasone	-	-	2%
Bortezomib/ Dexamethasone/ Panobinostat	7%	2%	1%
Bortezomib/ Panobinostat	-	2%	-
Dexamethasone/ Panobinostat	-	*	1%
Panobinostat	-	1%	1%

a – based on sample of 35 individual patient records collected during the 12-month specified period. b – based on sample of 161 individual patient records collected during the 12-month specified period within the time frame. C – based on sample of 295 individual patient records collected during the 12-month specified period within the time frame.

	From a clinical perspective the available data for PanVd suggests that this combination has less benefit for patients who have been exposed and are refractory to bortezomib. For this reason, alongside the toxicity issues mentioned above, PanVd is not used to a significant extent. In addition, in the UK, clinicians use bortezomib (V) extensively at first and second line. This means that when patients reach 3L and 4L, clinicians are less willing to retreat with bortezomib based regimens. Experts that we have consulted during the preparation of this appraisal have categorically stated that PanVd is not a relevant comparator (14,18). The ERG consulted three clinicians, one of whom also agreed with the view that PanVd is not a relevant comparator. Given our experience, it is not unreasonable to consider that a larger sample of experts would arrive at a different conclusion to the ERG and technical team regarding the appropriateness of PanVd as a comparator. For this reason, we urge NICE to seek further clinical expert opinion in order to resolve this issue and ensure that appropriate decisions are taken regarding the relevance of the comparators in this appraisal.
5. Is PANO/BORT/DEX a relevant comparator?	For reasons discussed under point 4, Sanofi do not believe PanVd to be a relevant comparator to IsaPd in the 4L setting.
Issue 4: Matched-adjusted indirect comparison	
6. Is the company's matched adjusted indirect comparison (MAIC) between ISA/POM/DEX and PANO/BORT/DEX valid?	The ERG raises five issues regarding the MAIC of IsaPd vs. PanVd. Each of these are addressed in turn below. 1. The ERG states that it is not clear if the covariates the company chose represent all relevant prognostic factors and treatment effect modifiers; if not, the results may be biased. Covariates included in the MAIC were necessarily limited to those reported in PANORAMA-2 and which were assessed in the ICARIA-MM trial. As noted in our submission, PANORAMA-1 and PANORAMA-2 were identified as relevant trials during the development of the MAIC but PANORAMA-2 was selected for inclusion in the MAIC because it has the most similar patient population to ICARIA-MM in terms of prior lenalidomide (Len) use: % of lenalidomide refractory patients was 98.2% compared to 38% on PanVd arm of PANORAMA-1 (20,21). In comparison, 92.3% of 4L patients on IsaPd were refractory to lenalidomide. A listing of baseline characteristics reported for PANORAMA-2 is provided below (Table 2), along with an indicator of whether this characteristic was assessed in the ICARIA-MM trial and whether the characteristic was included in the MAIC.

Table 2: Baseline characteristics reported for PANORAMA-2 Trial

Variable	Reported in ICARIA-MM	Included in MAIC
Sex	X	X
Age	X	X
ECOG performance status	X	X
Baseline serum albumin	X	
Baseline serum M protein		
Baseline urine M protein		
ISS staging	X	X
Ig subtype	X	
Light chain subtype	X	
FISH (cytogenetic abnormality)	X	X
Median time since diagnosis	X	X
Number of prior regimens	X	X
Number that previously received Bort	X	
Number that previously received Dex	X	

Number that previously received Len	X	X
Number that previously received Thal	X	
Prior ASCT	X	X
Median duration of prior Bort		
Number prior Bort regimens		
Progressed while on last Bort Regimen		
Progressed ≤60 day after last Bort regimen		
Bort in most recent prior regimen		
Dex in most recent prior regimen		
Dex in last Bort-containing regimen		
Best response at last treatment		

Input from the Sanofi clinical experts indicated that age, ISS stage, cytogenetic factors, prior stem cell transplant, and creatinine (renal status) could be considered as prognostic factors and refractory to Len and lines of prior therapies as treatment effect modifiers. For cases when effective sample sizes were too small, those variables not thought to be effect modifiers were considered for removal in the first instance. Based on these considerations, the following variables were included in the MAIC:

- Age (median)
- ECOG
- Gender

- The presence of one of Del17p, t(4;14) or t(14;16)
- ISS stage at study entry
- Number of previous therapies (median)
- Previous stem cell transplant
- Time since diagnosis (median)
- Prior treatment with Len

2. The ERG has concerns with the modelling including the way the treatment effect(s) were defined in the models and mixing baseline estimates from parametric models and estimates of treatment effects from Cox regression.

We are uncertain what specific concerns the ERG has regarding the survival modelling used in the MAIC of IsaPd vs. PanVd, as the general approach to estimation of parametric survival distributions and modelling of treatment effects (using "restricted" and "unrestricted" models) was the same as employed for the comparisons of IsaPd and Pd. With respect to "*mixing baseline estimates from parametric models and estimates of treatment effects from Cox regression*", we presume this relates to the application of HRs derived from the Cox regression in the MAIC to the survival distribution for IsaPd estimated using the unweighted data from ICARIA-MM. This issue is discussed below.

3. The ERG was also concerned about the use of hazard ratios from a Cox regression model in survival models that are not proportional hazards models.

We recognise the potential biases of using HRs for IsaPd vs. PanVd from a Cox regression in indirect treatment comparisons when the proportionality assumption is violated in one or more trials contributing to the comparison. With respect to the comparison of IsaPd vs. PanVd, the HRs estimated from the MAIC are applied to the parametric distributions for IsaPd. This approach requires the assumption that the hazards for PanVd are proportional to those of IsaPd. It *does not* require that the distribution to which the HRs is applied is a "proportional hazards" model (such as an exponential, Weibull, or Gompertz model). While the resultant distribution is not of the same class of distribution as the underlying distribution, if the underlying hazard is not a proportional hazards model (i.e., applying an HR to a lognormal distribution does not yield a lognormal distribution), it is unclear how this might bias the comparison.
In any case, it should be noted that for the base case, the distributions for TTD and OS, to which the comparison is most sensitive, are both exponential, which are proportional hazards models. Also, the test of Schoenfeld residuals for the

comparison of OS for IsaPd vs. PanVd in the MAIC was not statistically significant, suggesting that the assumption of proportionality for OS may not be unreasonable.

4. Furthermore, the ERG explains that the results of the MAIC may lack face validity because PanVd is estimated to have a shorter time to progression than Pd but is estimated to have a longer survival. PFS is typically correlated with OS as death is counted as an event in both metrics.

We agree with the ERG's assessment that the discordance of the results in terms of the estimated difference between PanVd vs Pd in PFS and OS raises questions regarding the face validity of the results of the MAIC of IsPd vs. PanVd.

5. The ERG rated the PANORAMA-2 trial (used to inform the comparison) moderate to poor in terms of trial quality (ERG report table 4), which adds to the uncertainty surrounding the MAIC.

We agree with the ERG's assessment of the quality of evidence from PANORAMA-2 and that this adds uncertainty to the comparison with IsaPd. However as noted, it was the best source of comparable evidence to ICARIA-MM and was chosen with this limitation in mind.

Issue 5: Subsequent treatments

7. What treatments are commonly used as a 5th line therapy in NHS clinical practice (not considering current CDF recommended drugs)?

In our base case, the percentage of patients receiving subsequent therapies were taken from the ICARIA-MM trial for both IsaPd and Pd arms (Table 3). Given the variety in medications administered post study, only the top 10 most frequently used medications were considered. For PanVd, they were assumed to be the same as for IsaPd, for consistency (See Appendix C). Also, in the base case, the duration of treatment with the post-study anti-cancer therapies was based on data from Kantar Health for Western Europe (22) and literature, if not available in Kantar Health.

Table 3: Proportion of patients receiving top ten subsequent anti-cancer treatments from ICARIA-MM trial

Subsequent anti-cancer treatment	Treatment arm	
	IsaPd	Pd

Bendamustine	10.71%	11.90%
Bortezomib	25.00%	16.67%
Carfilzomib	17.86%	21.43%
Daratumumab	7.14%	38.10%
Etoposide	10.71%	0.00%
Thalidomide	3.57%	0.00%
Lenalidomide	14.29%	2.38%
Melphalan	10.71%	0.00%
Panobinostat	3.57%	0.00%
Pomalidomide	7.14%	7.14%

Sanofi acknowledge that the post study treatments in ICARIA-MM may not reflect UK clinical practice at 5L. In particular, daratumumab use at 5L is unlikely given that NICE guidance recommends it at 4L only. Therefore, in our submission we presented two scenario analyses to test the cost impact of post study treatments on the ICER.

In the first case, we asked three UK clinical experts to comment on the distribution of subsequent treatments used in ICARIA (Table 4) in comparison to what are used in clinical practice (14). This feedback was used to inform the percentage of patients receiving subsequent therapies and the duration of these therapies in real-world UK clinical practice. In this scenario, where clinical expert feedback was implemented in the model, the ICER is £112,429.

It should be noted that the experts still considered that a small number of patients who had failed Pd or PanVd would receive daratumumab. In our response to Question 8, we have explored the impact of removing daratumumab or lenalidomide as subsequent therapies.

Table 4:Proportion of patients receiving subsequent anti-cancer treatments from UK clinical expert opinion

Subsequent anti-cancer treatment	**Treatment arm**	
	IsaPd	**Pd**
Bendamustine	13.31%	9.59%

	Bortezomib	25.23%	24.47%
	Carfilzomib	0.00%	0.00%
	Daratumumab	0.00%	17.50%
	Etoposide	3.13%	1.42%
	Thalidomide	20.00%	20.00%
	Lenalidomide	0.00%	0.00%
	Melphalan	11.78%	9.50%
	Panobinostat	17.82%	17.25%
	Pomalidomide	0.00%	0.00%

In a separate scenario, we also we applied the percentage of patients receiving subsequent therapies in the PanVd treatment arms, taken from the Dara NICE submission (TA510) (16) instead of the ICARIA-MM data. In this scenario, the ICER does not change in the IsaPd vs Pd comparison (since neither of these comparators have changes to their inputs), but it does change for the comparison of IsaPd vs PanVd (see Appendix C).

8. Do the subsequent treatments permitted in the ICARIA-MM trial impact on the generalisability of the overall survival data to clinical practice in the NHS?	As noted above, the post study use of daratumumab in ICARIA-MM is the most striking difference to UK clinical practice. There is also some post study use of lenalidomide. This is reflective of the global nature of the study but in the UK, daratumumab or lenalidomide are not routinely used after 4L. In response to the Technical report, we investigated the 4 general approaches for the adjustment of OS to reflect counterfactual assumptions regarding the use of subsequent therapies: 1. Rank preserving structural failure time (RPSFT) models 2. Two-stage method (TSE) 3. Markov Model Approach 4. Inverse probability of censoring weighting (IPCW)

Rank Preserving Structural Failure Time (RPSFT)

The RPSFT approach that can be used is appropriate when for adjusting OS for switching from control to active treatment, i.e. it is only applicable in cases where patients in the control arm are switching to the active therapy or to some other therapy that can be assumed to be equally effective as the active therapy. As this is not the case in this instance, the use of this method is not appropriate or relevant.

Two-Stage Estimation (TSE)

The TSE approach effectively combines PFS with PPS to obtain OS, with the PPS adjusted for the differences between treatment groups in use of post-progression therapies (19). The latter step is accomplished using a multivariable outcome model for PPS. The model for predicting PPS should also account for any baseline or time-dependent factors that may impact PPS or predict receipt of subsequent therapies. The latter might include, for example, time to progression.
For each patient, a counterfactual OS is then generated as the sum of the observed PFS and, for patient who progressed, the adjusted PPS. Because PPS is censored for some patients, it is generally appropriate to apply a re-censoring algorithm to PPS to avoid informative censoring. Such re-censoring has the effect of diminishing the amount of data available for projecting PPS and therefore OS. Once one has derived the adjusted OS data, one can then fit parametric distributions to the adjusted OS in order to project OS beyond the EOF in the trial. Thus, this approach requires fitting curves to both PPS and OS. Because of the complexities of this approach and the potential loss of data due to re-censoring, this method was not considered and instead a Markov cohort model approach, which is conceptually similar, was used instead (see below).

Markov Cohort Model (MCM) Approach

The TSE approach described above is conceptually similar to a non-homogeneous semi-Markov cohort model (MCM) with states for PFS and PPS. However, with the TSE approach, OS is calculated on an individual patient basis, whereas for a MCM, it is calculated at the cohort level. The MCM approach is relatively simple to implement compared with the TSE approach. Also, because the adjustment of PPS is not conducted at the patient-level, there is no need to apply a re-censoring algorithm to OS. It should be noted that with this approach, there is no need to do any curve fitting to OS, as OS is calculated in the Markov model. Rather this approach requires fitting two sets of curves, one for PFS and one for PPS. Since curves have already been fitted to PFS, only one additional curve fitting analysis is required for the MCM approach (compared with TSE which requires

two).

Given the advantages of the MCM over the TSE, we explored the use of the MCM approach to adjust OS for differences between the use of subsequent therapies in the ICARIA-MM trial and that expected in typical clinical practice based on feedback from UK clinical expert opinion as described above. In the Technical Engagement meeting, this was discussed with the ERG and NICE Technical Team and considered reasonable.

It should be noted that the TSE approach, combines information on PFS with estimated post-progression survival (PPS) to estimated OS. PPS is adjusted for receipt of post-progression therapy using multivariable regression. The TSE approach is premised on the assumption of a "second baseline" at disease progression. That is, prognosis upon progression is assumed to be more or less similar for all patients, or similar based on any baseline or secondary baseline covariates. While the TSE approach, and hence presumably the MCM approach, uses progression as a second baseline, in the IsaPd economic model, we included the costs of all "subsequent" treatments, defined as those treatments received *after discontinuation of therapy and not post-progression*, in our model. Hence, we have included costs for some treatments given post-discontinuation but pre-progression. To be consistent with the costs of subsequent therapies are considered in the model, we sought to combine estimates of TTD with adjusted post discontinuation survival (PDS) rather than combining PFS with adjusted PPS. Note that this deviates somewhat from the "second baseline" but is consistent with the original model. We believe this approach is not unreasonable for a scenario analysis given the strong correlation between PFS and TTD. Nevertheless, this is a potential limitation of the MCM (or the TSE) approach in this instance.

When assessing the feasibility of this approach, another important consideration is the number of observations available for the analysis and the number of covariates that would be required in the regression model for TTD. In this case, the numbers of patients who discontinued therapy is relatively small (N=28 and 42 in the IsaPd and Pd arms, respectively, or N=70 in total), and the number of potential subsequent treatments is relatively large, so that there is not likely to be sufficient data to reliably estimate the coefficients on each of the 10 drugs considered. A general rule of thumb is that there should be no less than 10 observations per covariate, which would suggest a maximum of 7 covariates if N=70. As noted above, we wished to adjust PDS in both arms to reflect the anticipated use of the subsequent therapies as suggested by the KOLs (Table 4). As shown in Table 4, there are 10 potential subsequent therapies to be considered. As it would be necessary to include a covariate for treatment group, and one would almost certainly want to include covariates for whether or not the patient had progressed, age (predictive of survival), and region (predictive of subsequent therapy), a regression analysis on PDS controlling for utilisation of all these

therapies would require 14 covariates. With only 70 patients, this yields far less than 10 observations per covariate. As shown in Table 5 below, the number of patients specific drugs post-discontinuation of study drugs is <10 for many treatments. Even dropping covariates for 5 of the drugs as well as covariates for age and region would require 7 covariates, which is the minimum recommended sample size and would yield results with a high degree of uncertainty.

Table 5: Number and percentage of patients receiving various drugs post-discontinuation

	N			%		
Subsequent treatments	**IsaPd**	**Pd**	**Total**	**IsaPd**	**Pd**	**Total**
Number of patients	28	42	70	-	-	-
Bendamustine	3	5	8	10.7%	11.9%	19.0%
Bortezomib	7	7	14	25.0%	16.7%	33.3%
Carfilzomib	5	9	14	17.9%	21.4%	33.3%
Daratumumab	2	16	18	7.1%	38.1%	42.9%
Etoposide	3	0	3	10.7%	0.0%	7.1%
Lenalidomide	4	1	5	14.3%	2.4%	11.9%
Melphalan	3	0	3	10.7%	0.0%	7.1%
Panobinostat	1	0	1	3.6%	0.0%	2.4%
Pomalidomide	2	3	5	7.1%	7.1%	11.9%
Thalidomide	1	0	1	3.6%	0.0%	2.4%

Given the limitations noted above with the MCM approach (and which also would likely apply to the TSE approach), and that the impact of assuming no post-discontinuation use of daratumumab or daratumumab and lenalidomide on OS were examined using the IPCW approach, the MCM approach was not implemented.

IPCW

A sensitivity analysis using IPCW methodology was conducted to evaluate the treatment effect on OS, in the absence of switch to subsequent anti-cancer therapy with daratumumab. The resulting HR was ***academic/commercial in confidence***

information removed which is consistent with the HR of 0.494 (95% CI; 0.240; 1.015) in the OS analysis for the 4L population, suggesting that daratumumab use post study did not influence the overall survival data (Table 6).

Table 6: ICARIA-MM secondary efficacy outcome – Sensitivity† analysis adjusting OS‡ for switch to daratumumab (4L population)

	Pd (N=58)	IsaPd (N=52)
Number (%) of deaths	***academic/commercial in confidence information removed***	
Number (%) of patients censored		
HR§ (95% CI) vs Pd		

†Estimated using IPCW method. ‡As per cut-off date: 11th October 2018. §HR<1 favours IsaPd arm. Abbreviations: CI, confidence interval; HR, hazard ratio; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; IPCW, inverse probability of censoring weighting; MM, multiple myeloma; OS, overall survival; Pd, pomalidomide, low-dose dexamethasone.

A second sensitivity analysis using IPCW methodology was conducted to evaluate the treatment effect on OS, in the absence of switch to subsequent anti-cancer therapy with daratumumab or lenalidomide (Table 7), the HR is ***academic/commercial in confidence information removed*** which is comparable to the HR without adjustment for either treatment (0.494 (95% CI; 0.240; 1.015)) suggesting that the results seen in ICARIA-MM 4L population are not impacted by choice of post study treatment of daratumumab and lenalidomide.

Table 7: IPCW method to adjust OS for daratumumab and lenalidomide post-study use

	Pd (N=58)	IsaPd (N=52)
Number (%) of deaths	***academic/commercial in confidence information removed***	
Number (%) of patients censored		
Hazard ratio (95% CI) vs Pd		

OS: Overall survival, CI: Confidence interval, HR: Hazard ratio. Cut-off date: 11th October 2018, Median follow-up time = 11.60 months. §HR<1 favors IsaPd arm

We have performed two exploratory scenario analyses in the model using the HRs for OS for IsaPd vs Pd based on the IPCW analyses above with informative censoring on receipt of daratumumab and receipt of daratumumab or lenalidomide.

Note that because the IPCW approach uses a panel data set with different weighted risk sets of patients over time rather than conventional time to event data, it is not straightforward to fit parametric survival distributions to the IPCW-adjusted survival data. Rather, it would require that individual patient data (IPD) be reconstructed from the weighted panel data set which could then be used to do the parametric curve fitting. The use of the HR from Cox model in the IPCW analysis eliminates the need for this additional step. The use of the HR from this analysis is appropriate because the base case OS curve for the 4L subgroup is exponential which is a proportional hazards model. In terms of costs of subsequent therapies, we have set the utilisation of daratumumab equal to 0% in the first analysis and the utilisation of daratumumab and lenalidomide to 0% in the second scenario. The results of these analyses vs Pd are provided below (Table 8,Table 9), and results versus PanVd are reported in Appendix C.

Table 8: ICER for IsaPd vs Pd with adjustment for daratumumab post study treatment

	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	ICER (deterministic) (£/QALY)
Sanofi updated base case (OS & TTD: Exponential; PFS: Lognormal (R))							
IsaPd	***Academic/commercial in confidence information removed***						
Pd							

Table 9: ICER for IsaPd vs Pd with adjustment for daratumumab and lenalidomide post study treatment

	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	ICER (deterministic) (£/QALY)

	Sanofi updated base case (OS & TTD: Exponential; PFS: Lognormal (R))
	IsaPd — ***Academic/commercial in confidence information removed***
	Pd

Summary

According to experts we have consulted, post study treatments are unlikely to influence the outcomes seen in ICARIA-MM because patients at 5L and beyond are very ill and nearing the end of life where treatment options are limited and mainly palliative. Results of IPCW analyses of OS in which patients who received daratumumab or lenalidomide post-discontinuation of study therapy were informatively censored generally confirm expert opinion as the HRs for OS from these analyses were qualitatively similar to that from analyses without adjustment of 0.494 (95% CI; 0.240; 1.015).

Use of other approaches to adjust OS such as the RPSFT approach, TSE, or an MCM were deemed either infeasible due to small numbers and a multiplicity of required covariates in the regression model for PDS (MCM and TSE) or inappropriate (RPSFT). Despite the similarity of the results in these analyses for post study adjustments, these results should be interpreted with caution as all factors contributing to the shift to daratumumab or lenalidomide may have not been captured in the IPCW model.

Further the relatively small patient numbers on which to extrapolate long term outcomes (70% - 80% censored patients and results based on 10 to 16 patients) in the economic model means that ICER estimates are unlikely to be robust. Therefore, the analyses reported above can only be considered exploratory. Unlike the RPSFT approach, the IPCW approach (and the MCM and TS approaches) is not randomisation based and therefore is likely to be biased by unmeasured factors that are associated with receipt of daratumumab or lenalidomide and survival. Results from, or based on, the IPCW analyses therefore should be interpreted very cautiously.

Issue 6: Extrapolation of overall survival, progression-free survival and time to treatment discontinuation	
9. How robust is the extrapolation of overall	In the ERG's view, the company base case selections for distributions of overall survival, PFS and TTD were all considered

survival, progression-free survival and time to treatment discontinuation?

reasonable. Indeed, the ERG stated that if no other curve fits could be examined then they would choose the distributions selected by Sanofi. However, as requested, we have tested a number of alternate extrapolations. The clinical plausibility of these extrapolations are discussed in question 10 below. Empirical hazards plot and hazard ratio and quantile plots for the base case have been provided in Appendix B to this response.

In light of the high censored data and the uncertainty of long-term extrapolations at 4L, we have reported the deterministic ICERs vs Pd as being the most appropriate for decision making until further data collection is performed via CDF (Table 10,Table 11,Table 12).

Table 10: Sensitivity analyses for overall survival, IsaPd vs Pd (Isa @ *academic/commercial in confidence information removed* PAS discount, all other compounds at list price)

Option	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	ICER (£/QALY) (deterministic)
Sanofi updated base case (OS & TTD: Exponential; PFS: Lognormal R)							
IsaPd	***academic/commercial in confidence information removed***			1.689	1.102	113,179	**102,725**
Pd				-	-	-	**-**
Sensitivity analysis 1a: Use of a jointly-fitted lognormal (R) model for OS							
IsaPd	***academic/commercial in confidence information removed***			1.701	1.108	113,203	**102,125**
Pd				-	-	-	-
Sensitivity analysis 1b: Use of a jointly-fitted log-logistic (R) model for OS							
IsaPd	***academic/commercial in confidence information removed***			1.397	0.923	112,598	**122,055**
Pd				-	-	-	-
Sensitivity analysis 2a: Use of a jointly-fitted Weibull (R) model for OS							
IsaPd	***academic/commercial in confidence information removed***			1.144	0.769	112,094	**145,859**
Pd				-	-	-	-
Sensitivity analysis 2b: Use of a jointly-fitted Gen Gamma (R) model for OS							
IsaPd	***academic/commercial in confidence***			1.773	1.153	113,346	**98,339**

Pd	***information removed***	-	-	-	-
Sensitivity analysis 2c: Use of a jointly-fitted RSC Weibull (R) model for OS					
IsaPd	***academic/commercial in confidence information removed***	2.284	1.467	114,364	**77,973**
Pd		-	-	-	-

Table 11: Sensitivity analyses for PFS, IsaPd vs Pd (Isa @ *academic/commercial in confidence information removed* PAS discount, all other compounds at list price)

Option	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	ICER (£/QALY) (deterministic)
Sensitivity analysis 3a: Use of an exponential model for PFS							
IsaPd	***academic/commercial in confidence information removed***			1.689	1.091	113,179	**103,736**
Pd				-	-	-	-
Sensitivity analysis 3b: Use of a jointly-fitted Weibull (R) model for PFS							
IsaPd	***academic/commercial in confidence information removed***			1.689	1.080	113,179	**104,811**
Pd				-	-	-	-
Sensitivity analysis 3c: Use of a jointly-fitted RCS Weibull (R) model for PFS							
IsaPd	***academic/commercial in confidence information removed***			1.689	1.116	113,179	**101,377**
Pd				-	-	-	-

Table 12: Sensitivity analyses for TTD, IsaPd vs Pd (Isa @ *academic/commercial in confidence information removed* PAS discount, all other compounds at list price)

Option	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	ICER (£/QALY) (deterministic)
Sensitivity analysis 1: Use of an exponential model for TTD (base case)							
IsaPd	***academic/commercial in confidence information removed***			1.689	1.102	113,179	**102,725**
Pd				-	-	-	**-**

	Sensitivity analysis 2: Use of a jointly-fitted log-logistic (R) model for TTD					
	IsaPd	***academic/commercial in confidence information removed***	1.689	1.102	197,982	**179,696**
	Pd		-	-	-	-
	Sensitivity analysis 3: Use of a jointly-fitted Gompertz (R) for TTD					
	IsaPd	***academic/commercial in confidence information removed***	1.689	1.102	147,876	**134,217**
	Pd					
	Sensitivity analysis 4: Use of a jointly-fitted lognormal (R) model for TTD					
	IsaPd	***academic/commercial in confidence information removed***	1.689	1.102	216,033	**196,079**
	Pd		-	-	-	-
	Sensitivity analysis 5: Use of a jointly-fitted Weibull (R) model for TTD					
	IsaPd	***academic/commercial in confidence information removed***	1.689	1.102	116,417	**105,664**
	Pd		-	-	-	-

We have also provided analyses for the PanVd comparisons in Appendix C although we do not agree that this is a relevant comparator in this appraisal.

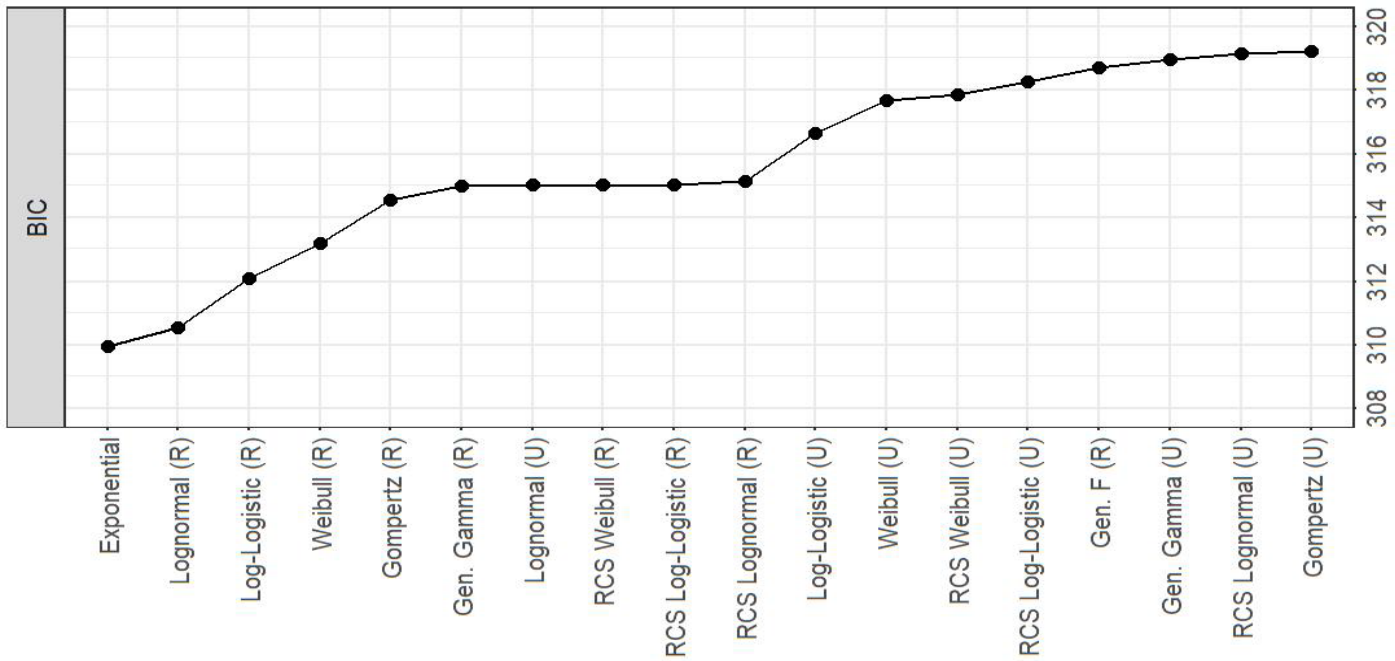
10. How informative is the ERG's sensitivity analysis regarding the extrapolation of overall survival, progression-free survival and time to treatment discontinuation?

Overall survival

As agreed by the ERG the base case uses the exponential distribution to estimate long term survival for patients treated with IsaPd or Pd. This distribution was selected because it had the best statistical goodness of fit (lowest BIC), acceptable visual fit and projections of OS that were clinically plausible and consistent with long-term OS data from pivotal trial for Pd (MM-003), though possibly underestimates OS for IsaPd at the tail of the distribution over the trial period. The patient population on which these projections are based are typically younger and fitter and therefore have a better prognosis than patients expected in routine practice.

The exponential distribution was considered reasonable by ERG and the Technical team, but sensitivity analyses were presented using lognormal (R), Log-logistic (R) and Weibull (R) for overall survival. In Figure 2 below, of the two, Log-logistic has a lower BIC (better statistical fit) than Weibull (R).

Figure 2: Fit statistics for parametric distributions fit to OS for the 4L population of ICARIA-MM

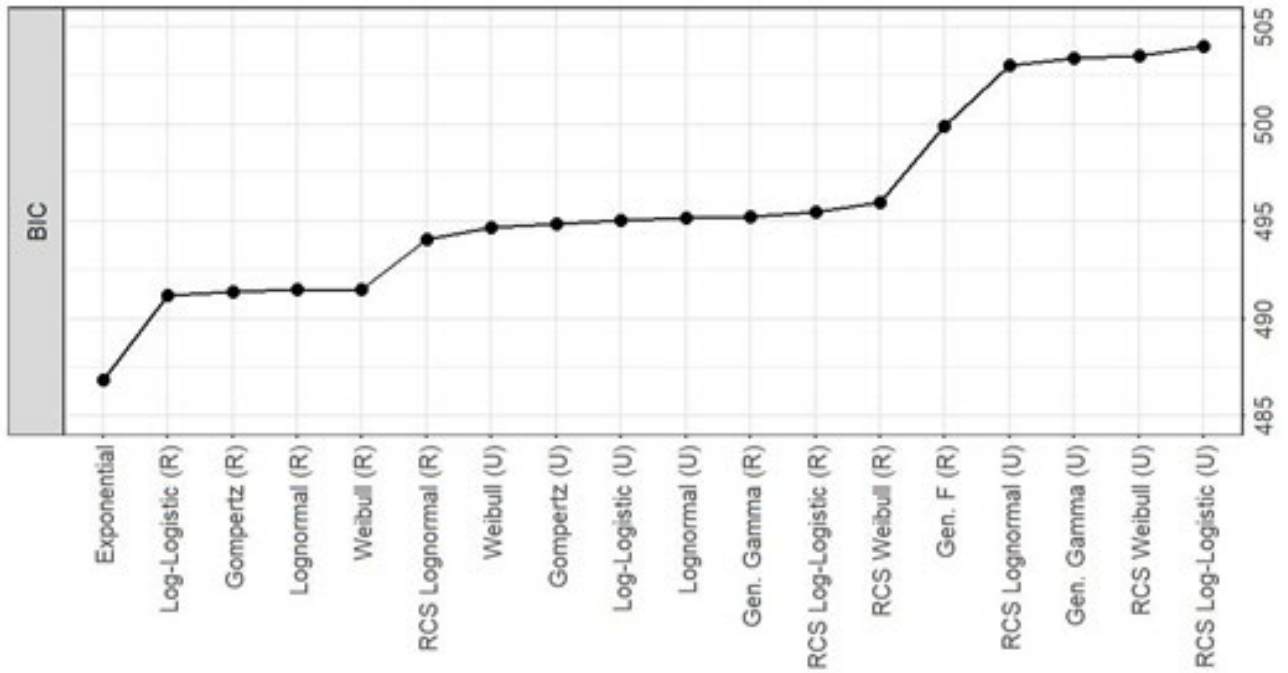


There are limited long-term data on OS in patients similar to those in the 4L subgroup of ICARIA-MM with which to compare the external validity of these projections. At 28 months, the maximum reported follow-up of the MM-003 trial, OS for Pd patients was approximately 15% (15). In contrast, the exponential, lognormal (R) and log-logistic (R) distributions project OS of approximately 30% at 28 months; the Weibull (R) and Gompertz (R) project OS of approximately 20% at 28 months and the generalised gamma (R) distribution projects OS of approximately 40% at 28 months. Weibull (R) predicted >30% survival probability at 28 months.

Although the parametric distributions project OS for Pd at 28 months that is greater than that observed in the MM-003 trial, as noted above, the KM survival distribution for PFS for Pd patients in the MM-003 trial was below that for Pd patients in the 4L subgroup of ICARIA-MM, suggesting the former had poorer prognosis than the latter.

	A similar finding is observed when comparing the OS for Pd patients in the two arms. Although the median OS for the Pd arm of the MM-0003 trial (13.1 months) (15) was only slightly lower than that in the 4L subgroup of ICARIA-MM (approximately 14.3 months), the latter was heavily influenced by two deaths between 13 and 14 months at which point there were only approximately 10 patients remaining at risk, resulting in a 20% decline in the PFS at that point. A comparison of the KM curves for OS for the Pd arm of MM-003 and the 4L subgroup of ICARIA-MM clearly suggest worse survival for Pd patients in the former than the latter. Given the better prognosis of Pd patients in the ICARIA-MM trial, the more favourable long-term projections based on the exponential distribution do not seem unreasonable. Given that 60.3% on Pd arm and 78.8% on the IsaPd arm were censored, and limited real-world evidence on long term outcomes in 4L is available, further clinical validation was sought for the purposes of this response from a group of three NHS consultant haematologists (18). This was in addition to the validation exercise carried out for the original submission (14). All three experts commented on the ITT population OS curves. In all cases the exponential fit was chosen within the top three preferred curves. Two experts selected Weibull (R) as their preferred choice for OS in the ITT population and one expert selected exponential as their preferred choice. We were able to seek further advice from two of these experts about the extrapolations at 4L. In this setting, the exponential fit was chosen unequivocally by one clinician and the other felt that whilst long term survival is unusual in this setting, it cannot be ruled out, making the exponential curve a good 2nd option. However, given the less optimistic nature of the Weibull (R) curve, this was their conservative first choice. This clinician noted that some patients can experience prolonged response from anti-CD38 therapy so the longer tail predicted by exponential curve for IsaPd may be possible (18). Weibull (R) tends to be a typical choice for overall survival in cancer, but in the estimated Weibull (R) extrapolations fitted to the ICARIA-MM study, almost all patients are dead by 5 years in the Pd arm and by 10 years on IsaPd. This is not consistent with the clinical expert feedback and published evidence regarding long term survival for a small proportion of patients with RRMM. Selection by the clinical experts of the Weibull (R) curve did not generally take into account the better prognosis for younger and fitter patients, some of whom are present in the data set and should be considered overall in decision making at the population level. The exponential curve predicts around 10% of patients alive at 10 years on isatuximab and all dead by 15 years. In the pomalidomide arm, almost all patients are dead by 10 years estimated by the exponential fit. Clinical experts said that the tail end of the curve is difficult to predict but a few patients (around 1-5%) will remain alive at 15 years. This is because some patients whose disease progresses more slowly, will do much better than those whose disease is rapidly progressing and most,

	but not all patients will have died within 15 years (18). **PFS** As with overall survival, there are no long-term data on PFS for patients similar to those in ICARIA-MM that can be used to assess the validity of long-term projections. However, there are less censored data for PFS: 43.1% of Pd and 55.8% of IsaPd patients. Therefore, the base case choice, selected again based on best statistical fit and visual fit is plausible. Data for PFS for Pd out to approximately 75 months are available from the MM-003 trial. Median observed PFS for Pd in this trial (16 weeks = 3.7 months) was substantially less than that for patients receiving Pd in the subgroup of patients in ICARIA-MM receiving 4L treatment (approximately 7.5 months) (15). In the clinical validation exercise with NHS consultant haematologists, there was no consensus amongst the respondents on the preferred estimation for PFS, however there was a general agreement on the top three curves. The RCS Weibull (R), Weibull (R), and exponential curves appeared to be the preferred options, and one KOL also included Gompertz (R) in the top three. These were tested in sensitivity analysis above (Table 11). **TTD** The data for TTD have less censoring. 27.6% and 45.1% of patients receiving Pd and IsaPd respectively were censored. Therefore, long term parametric extrapolation selected is based on more available data. The exponential distribution was selected as this distribution has the lowest BIC, good visual fit, and the test of linearity of Schoenfeld residuals suggest that the PH assumption (required by exponential distribution) is not violated. It should be noted that the exponential model has the lowest BIC value, which is nearly 5 points lower than the remaining models, including log-logistic (tested in ERG sensitivity analyses) (Figure 3). **Figure 3: Fit statistics for parametric distributions fit to TTD for the 4L population of ICARIA-MM**

	
Issue 7: Time horizon	
11. Over what time horizon would you expect all differences in benefits and costs that arise as a consequence of treatment choice to materialise?	As noted above, the clinical experts with whom we consulted, almost all agreed that 15 years is a reasonable time-horizon to capture life expectancy of patients at 4L. However, as some suggested that few live longer (see response to issue 6), we have adopted a 20-year time horizon in the base case (14,18). This is in line with the changes from the ERG and Technical Team.

Issue 8: Cost uncertainties in the analysis

12. Do the differences in the relative dose intensities in the ISA/POM/DEX and POM/DEX arms of the ICARIA-MM trial impact on the robustness of the cost-effectiveness estimates?

RDI of Pd is lower on IsaPd than Pd. This is because dose reductions of isatuximab were not permitted in the ICARIA-MM trial, but dose omissions were, for example in response to G4 neutropenia. Pomalidomide was given as per the SPC and dose reductions of pomalidomide are permitted, for example in response to neutropenia.

In the ICARIA trial more neutropenia was observed in the triplet IsaPd arm and so one would expect a greater level of dose reductions or dose omissions compared to Pd alone. Applying 100% dose intensity on all medications increases the base case ICER to £110,891 (Table 13).

Table 13: Base case cost-effectiveness with differential RDIs removed (i.e. 100% RDI applied for all medications)

	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	ICER (deterministic) (£/QALY)
Sanofi updated base case (OS & TTD: Exponential; PFS: Lognormal) with 100% RDI for all medications							
IsaPd	***academic/commercial in confidence information removed***			1.689	1.102	122,176	**110,891**
Pd				-	-	-	

13. Is the assumption of no drug wastage reasonable?

The base case includes wastage in line with previous HTA submissions. Removing impact of wastage reduces the base case ICER to £83,159

14. Are the costs of treatment underestimated in the company model?

These have been addressed in the updated model. Medications are now costed at the start of regimen cycle (conservative assumption) and applies to all comparators as well as subsequent treatments. The use of GCSF have now been taken from ICARIA-MM trial.

Issue 9: Health utility values

15. Are the utility values included in the

In the updated model, health state utilities are now varied in the PSA via bootstrap. This will ensure that PPS does not exceed that of PFS. Whilst there is no guarantee that the utility value for PPS will This will ensure that PPS does not exceed that of

company model appropriate?	PFS within any given sample, the utility values for each simulation are estimated using the same bootstrap sample ensuring that there is appropriate correlation of the utility values across samples. In the Technical Engagement meeting, this was discussed with the ERG and NICE Technical Team and considered reasonable.
Issue 10: Cancer Drugs Fund	
16. Is there further data being collected that could reduce uncertainty surrounding longer-term effectiveness and health outcomes in the relevant population(s)?	We strongly support the use of the CDF to resolve key uncertainties in the evidence base for this appraisal. Data being collected at the moment and also potentially collected via the CDF will help to address the following outstanding uncertainties with this case. • **Immature overall survival data where there are substantial numbers of censored patients:** The ongoing data collection for patients enrolled in ICARIA-MM will provide more critical evidence for survival as would enrolment into the CDF • **Real world evidence to describe 4L patients and their outcomes**: There is a paucity of evidence at 4L in the UK. Collecting data for use of IsaPd to describe both the baseline characteristics of treated patients and their outcomes in the real-world UK clinical setting will provide important information for future decision making. The current EAMS scheme (projected to enrol around 80 patients) is providing limited data through the enrolment criteria and we would expect these patients to continue into the SACT database during a period in the CDF. • **Understanding outcomes for patients re-treated with anti-CD38**: We acknowledge that there is no evidence to support anti-CD38 retreatment, particularly as daratumumab at 2L is a relatively new innovation and it is only recently that patients treated with it may be reaching 4L. However, we agree with the opinions of the clinical experts consulted about this and have argued in issue 2 above that patients who have previously received an anti-CD38 therapy but who did not progress or indeed those patients for whom there has been an intervening line of treatment, may be able to

	benefit from isatuximab at 4L. Recall this is due to the differing target epitopes on the cell surface for daratumumab and isatuximab, the different combination partners for daratumumab at 2L and isatuximab at 4L and the possibility that pomalidomide could be a superior IMiD to lenalidomide. We are undertaking a pathway study using the HES data to map 1L and 2L patients, their treatments, outcomes and resource use in the UK setting which will help to describe the current paradigm in earlier lines of treatment. By placing this in the context of the RWE described above and data collection for new patients entering the SACT database during a period in the CDF we hope to be able to provide more information to inform the retreatment debate. For this strategy to be successful it is important that the recommendation for isatuximab to enter the CDF should include provision for patients who are not naïve to daratumumab at 2L.
17. When will these additional data become available?	The emerging data and proposed data collection opportunities discussed above are likely to be available either during or at the conclusion of the 2 to 3-year timeframe offered by the CDF but not within the timeframe of the current appraisal. The critically important assessment of overall survival will require the full duration of the CDF to compare outcomes of ICARIA-MM trial with real-world patients and to provide more confidence about which long-term extrapolation of overall survival is appropriate.
18. How suitable is the technology for use in the Cancer Drugs Fund (CDF)?	Clinical uncertainty is evident from the high level of censoring in ICARIA-MM. As discussed above this will be addressed during the CDF period making isatuximab a suitable candidate for use in the CDF. Notably, the continuing collection of survival data during follow up to ICARIA-MM and data entry into the SACT database to establish the real-world outcomes for MM patients at 4L in England as part of a CDF agreement will ensure that the uncertainty surrounding longer-term effectiveness and health outcomes can be addressed. The plausibility of reaching a cost-effective ICER making isatuximab suitable for entry into the CDF is driven largely by the drug acquisition cost of isatuximab and pomalidomide. Sanofi is committed to working with NICE and NHSE and so we have agreed an updated PAS on invoice discount of ***academic/commercial in confidence information removed*** with PASLU for isatuximab. ***academic/commercial in confidence information removed*** Below (Table 14) is a summary of the updated base case ICER including the ***academic/commercial in confidence information removed*** PAS for isatuximab and with pomalidomide at list price. **Table 14: Base case cost-effectiveness results with *academic/commercial in confidence information removed* discount applied for isatuximab**

	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	ICER (deterministic) (£/QALY)
Sanofi updated base case (OS & TTD: Exponential; PFS: Lognormal (R))							
IsaPd	***academic/commercial in confidence information removed***			1.689	1.102	113,179	**102, 725**
Pd				-	-	-	**-**

All ICERs in this response, including the sensitivity analyses to account for alternate extrapolations of overall survival, PFS and TTD presented in Issue 6 above, reflect this increased on invoice discount of ***academic/commercial in confidence information removed*** for isatuximab. According to the expectations of the ERG we have maintained list prices for all other comparators and subsequent treatments

Academic/commercial in confidence information removed

We recognise that the ICERs tabulated here are above the commonly accepted willingness to pay threshold for end of life treatments. However, these figures incorporate list prices for pomalidomide and subsequent treatments. Whilst we are unaware of their associated discounts, we are confident that the 'true' ICER will provide assurance to the committee that isatuximab in combination with pomalidomide for the treatment of multiple myeloma does have the potential to represent good value for money to the NHS in the 4L setting where there remains high unmet need and so should be considered for entry into the CDF. It is important to recognise that the deterministic ICERs presented above are the most appropriate for decision making purposes where uncertainty can be subsequently addressed by a period in the CDF.

Issue 11: End of Life

19. Under standard care, is the life expectancy of adults with relapsed or refractory multiple

All the clinical experts we spoke with all agree that life expectancy for patients at 4L is less than 2 years (14,18). Real-world evidence for current treatment options in UK patients with median of 3-5 prior lines of treatment including lenalidomide and PI are shown below (Table 19).

Table 15: PFS and OS in patients who received 3 prior lines of treatment

myeloma after 3 prior treatments less than 24 months?

Treatment	IsaPd	Pd	Pd	Pd	Pd	Pd
Source	**ICARIA-MM**		**RWE[1]**	**RWE[2]**	**RWE[3]**	**MM-003**
% prior lenalidomide	**92.3%**	**87.9%**	**100%**	**87%**	**100%**	**94.7%**
Median number of prior lines/therapies	**3**	**3**	**3**	**4**	**4**	**5**
Median PFS (months)	13.3	7.8	3.4	8.0	4.3	4.0
Median OS (months)	Media not reached in the ICARIA-MM trial	14.4	10.9	8.6	13.7	13.1

RWE[1], real world evidence UK study, Miles & Wells 2015 (23); RWE[2], real world evidence study reported in TA427 (conducted by Celgene) (15); RWE[3] – real world evidence study in UK by Maciocia 2015 (24); TA510 (16), Abbreviations: IsaPd, isatuximab+ pomalidomide+ dexamethasone; Pd, pomalidomide+ dexamethasone; RWE, real-world evidence.

Mean survival (deterministic) of Pd in the company model using different parametric distributions for overall survival are shown below (Table 20). It should be noted that the model predictions are based on the trial population of ICARIA but does shows that exponential is most closely reflective of Pd clinical benefit.

Table 16: Mean survival (deterministic) of Pd in the company model using different parametric distributions for overall survival

Distribution	LYG on Pd
Exponential (base case)	***academic/commercial in confidence information removed***
Lognormal	
Loglogistic	
Gompertz	
RSC Weibull	
Weibull (R)	
Gen Gamma	

20. Does ISA/POM/DEX extend life for more than 3 months compared with standard care for adults with relapsed or refractory multiple myeloma after 3 prior treatments?	Whilst the overall survival data is immature from ICARIA-MM it is clear that the IsaPd combination will provide considerably more life extension that Pd. It is known that PFS is correlated with OS (25, 26). PFS in the IsaPd arm of ICARIA-MM at 4L is 13.3 months compared to 7.8 months for patients treated with Pd. This represents an additional progression-free period of 5.5 months in patients who have received 3 prior lines of treatment. The base case economic modelling estimates that median OS in the IsaPd arm could be 33.3 months. This compares with the observed median OS in the Pd arm of ICARIA-MM of 14.4 months suggesting that isatuximab in this treatment setting provides substantial survival benefit for patients who are heavily pre-treated and significantly burdened by disease with short life expectancy under current treatment options.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Technical engagement response

Appendices

Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma

[ID1477]

9 April 2020

File name	Version	Contains confidential information	Date
ID1477_Isatuximab_Technical engagement response_ Appendices_09042020_ FINAL_REDACTED	FINAL	No	9th April 2020

Contents

Appendix A: Change log of model edit and updates (since 10 March 2020)

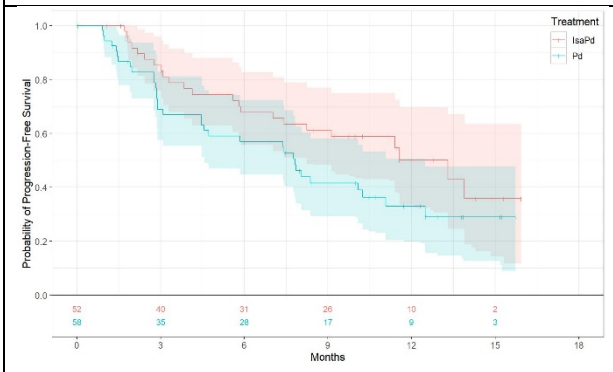
- Added the possibility to sample health state utilities in the PSA via a bootstrapped distribution. The health state utilities are now being varied in this fashion.
- Changed the way medication costs are assigned; previously an average weekly cost per regimen cycle was calculated, the model has now been changed to assign the full cost of the regimen cycle at the first week. This method is more accurate as the prior method slightly underestimated costs. This change affects all comparator regimens as well as the subsequent therapies
- Fixed an error incorrectly causing terminal costs not to be varied in the PSA. Minimal impact on PSA results.
- Added two additional scenarios to the list of scenario analyses of "4th Line (Basecase)". These are listed as "No Dara Subsequent Tx – IPCW HR OS" and "No Dara or Len Subsequent Tx – IPCW HR OS"
- Updated all entered PAS for IsaPd in the model to *academic/commercial in confidence information removed*
- Updated high/low DSA values for terminal decrement in utility

Appendix B: Diagnostic tests for curve selection in the base case (Empirical hazards plot and hazard ratio and quantile plots)

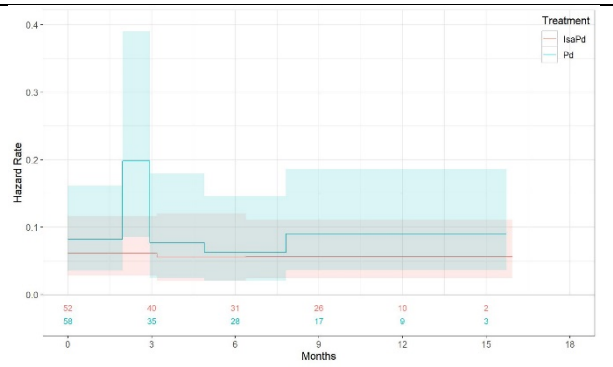
B.1 Progression free survival (PFS)

Figure 1: Progression-free survival for the 4th line population of ICARIA-MM, by randomised treatment

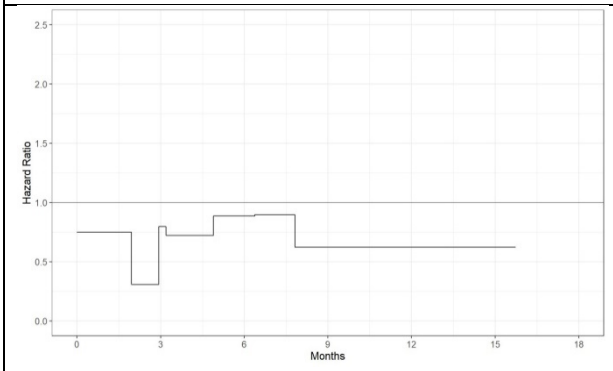
A. Kaplan-Meier Survival Distribution



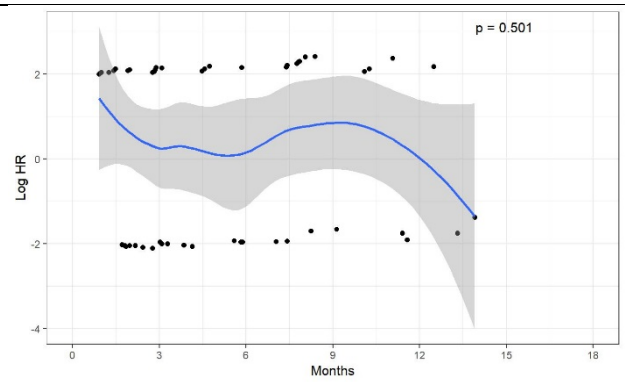
B. Hazard Rates



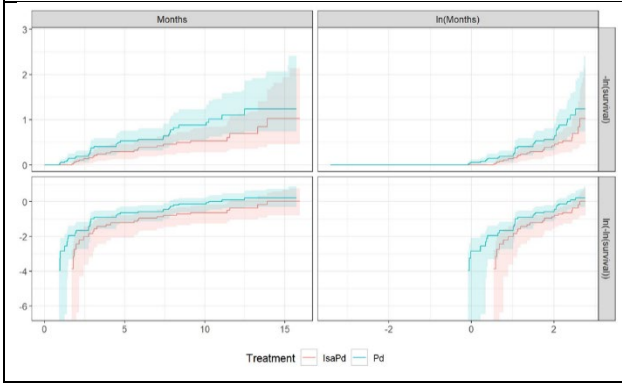
C. Hazard Ratio



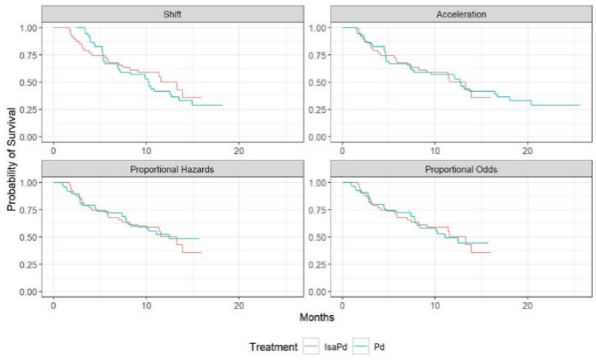
D. Schoenfeld Residuals



E. Transformation Diagnostics



F. AFT Treatment Effect Diagnostics

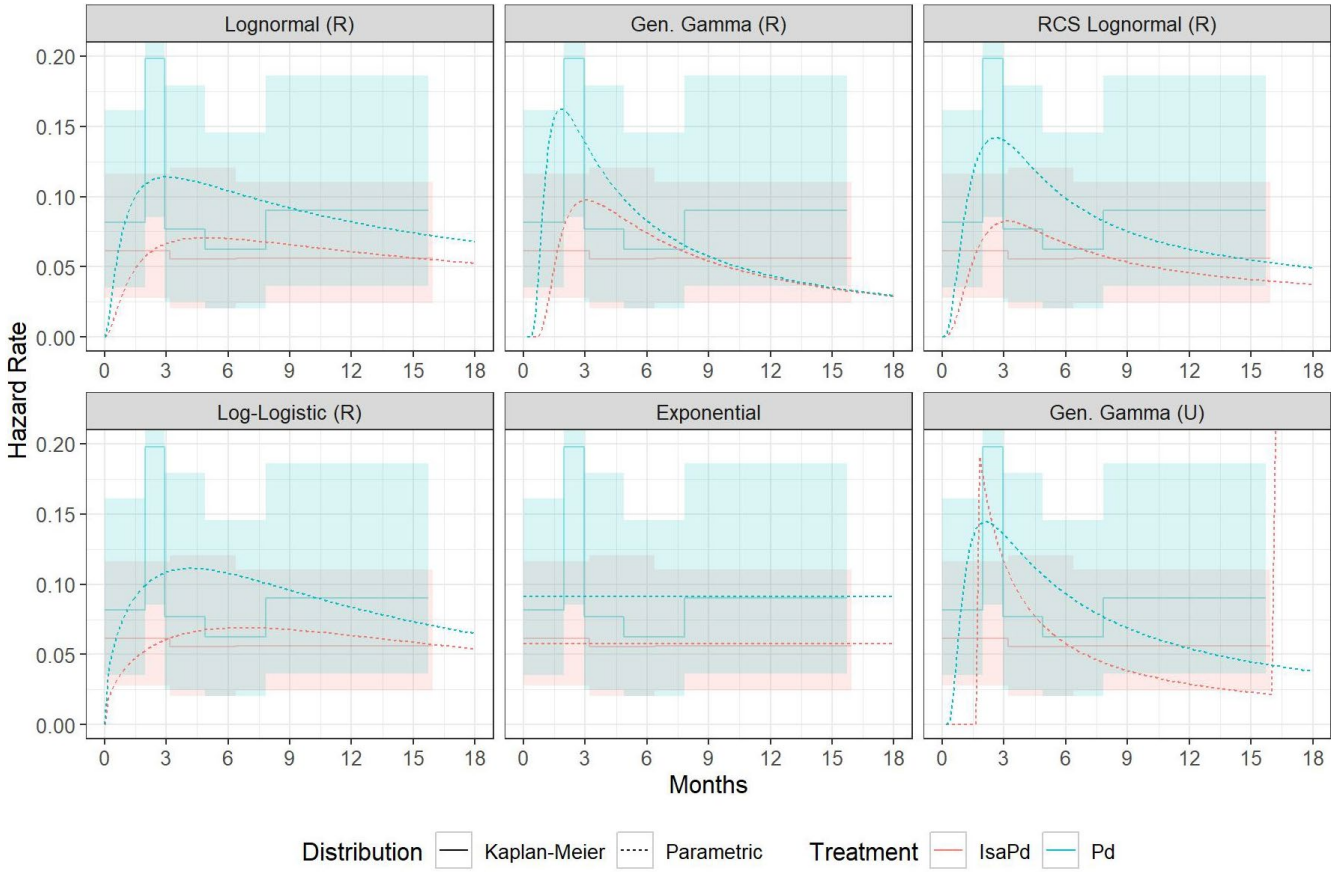


Abbreviations: AFT, accelerated failure time; HR, hazard ratio; IsaPd; isatuximab with pomalidomide and dexamethasone; Pd, pomalidomide with dexamethasone.

Hazard rates during the trial follow-up for the top six best fitting parametric survival distributions based on BIC for PFS are compared with non-parametric hazards in Figure 2.

The majority of the top six best fitting distributions yield hazard rates that increase initially and then decrease over time. For the majority of the top six distributions, the hazard for IsaPd is projected to be lower than that for Pd throughout the trial follow-up. The exponential distribution provides the best match overall to the empirical hazards.

Figure 2: Hazard rates for parametric survival distributions fit to PFS for the 4th line population from ICARIA-MM, by randomised treatment



Abbreviations: IsaPd; isatuximab with pomalidomide and dexamethasone; Pd, pomalidomide with dexamethasone; PFS, progression-free survival; R, restricted; RCS, restricted cubic spline; U, unrestricted.

RSMT for PFS to end of trial follow-up and 15 years are shown in Table 1. Projected RMST for PFS after 15 years with Pd ranges from 10 months (restricted Weibull) to 30 months (restricted generalised F and generalised gamma). For IsaPd, RMST at 15 years ranges from 10.4 months (unrestricted generalised gamma) to 38.6 months (restricted generalised F and generalised gamma). The restricted lognormal distribution yields a projected RMST at 15 years for IsaPd (20.8 months) that is approximately in the middle of the range of estimates from the various distributions considered. The projected difference in RMST for IsaPd versus Pd in PFS through 15 years ranges from -13.2 to 13.3 months. The difference in RMST for IsaPd versus Pd in PFS through 15 years for the restricted lognormal distribution is 7.6 months, which is also approximately in the middle of the range of estimates.

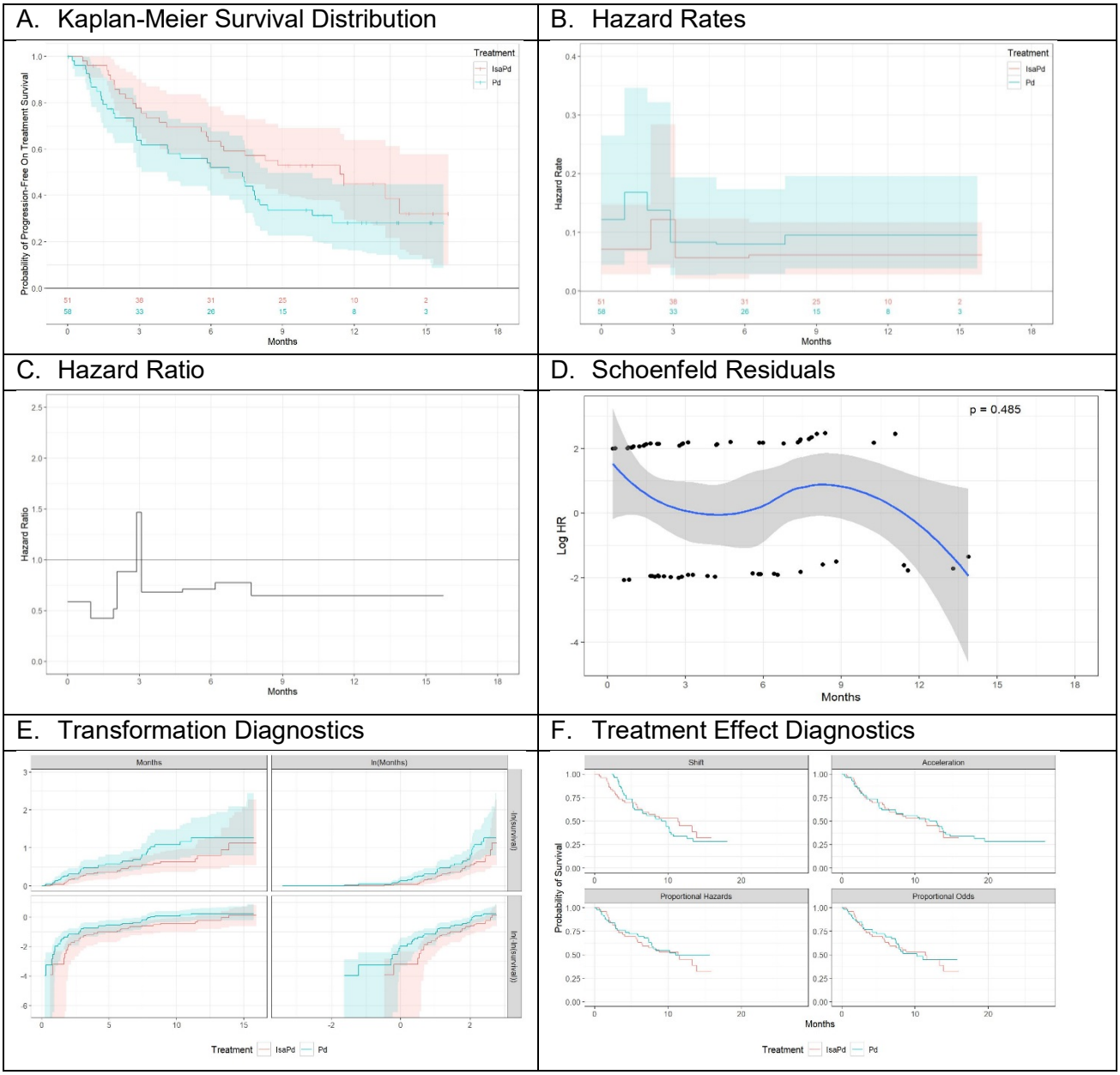
Table 1: RMST for PFS to End of Trial follow-up and 15 years among the 4L population of ICARIA-MM, by randomised treatment arm

Distribution	End of Trial follow-up			15 years		
	IsaPd	Pd	Difference	IsaPd	Pd	Difference
Kaplan-Meier	10.1	8.1	2.0			
Exponential	10.3	8.3	2.0	17.3	10.9	6.4
Gen. F (R)	10.2	8.4	1.8	38.6	30	8.6
Gen. Gamma (R)	10.2	8.4	1.8	38.6	30	8.6
Gen. Gamma (U)	10.2	8.3	1.9	10.4	23.6	-13.2
Gompertz (R)	10.4	8.4	2.0	15.4	10.3	5.1
Gompertz (U)	10.4	8.3	2.1	13.6	11.4	2.2
Log-Logistic (R)	10.1	8.1	2.0	22	14.5	7.5
Log-Logistic (U)	10.4	8.2	2.2	21.4	14.8	6.6
Lognormal (R)	10.4	8.2	2.2	20.8	13.2	7.6
Lognormal (U)	10.4	8.3	2.1	20.2	13.5	6.7
RCS Log-Logistic (R)	10.4	8.3	2.1	30.6	19.6	11
RCS Log-Logistic (U)	10.4	8.3	2.1	32	19.4	12.6
RCS Lognormal (R)	10.3	8.3	2.0	28.3	16.9	11.4
RCS Lognormal (U)	10.4	8.2	2.2	30	16.7	13.3
RCS Weibull (R)	10.3	8.3	2.0	22.2	12.6	9.6
RCS Weibull (U)	10.3	8.3	2.0	20.9	13.3	7.6
Weibull (R)	10.4	8.3	2.1	15	10	5
Weibull (U)	10.4	8.4	2.0	14.2	10.2	4
Min	10.1	8.1	1.8	10.4	10.0	-13.2
Max	10.4	8.4	2.2	38.6	30.0	13.3

Abbreviation: PFS, progression-free survival; RMST, restricted mean survival time.

B.2 Progression-free on treatment

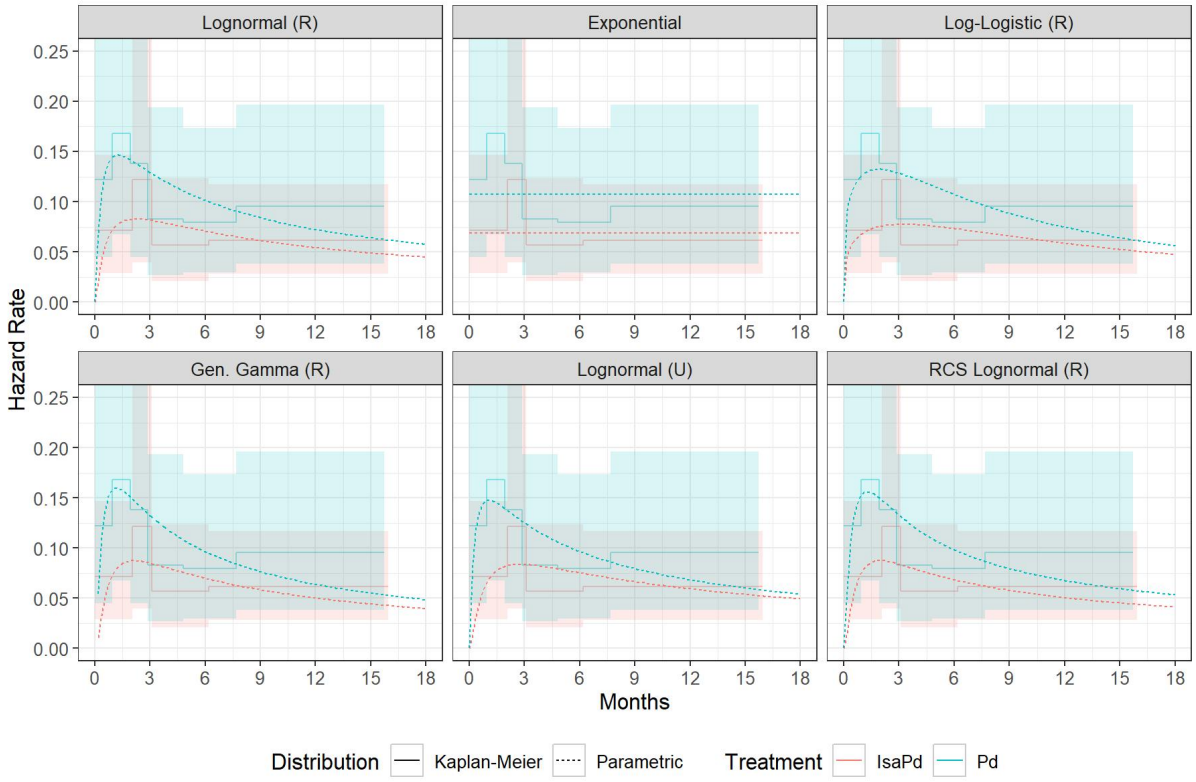
Figure 3: PFS on treatment for the 4th line population of ICARIA-MM, by randomised treatment



Abbreviations: HR, hazard ratio; IsaPd; isatuximab with pomalidomide and dexamethasone; Pd, pomalidomide with dexamethasone; PFS, progression-free survival.

Hazard rates during the trial follow-up for PFS on treatment for the top six best fitting parametric survival distributions are compared with non-parametric hazards in Figure 4. With the exception of the exponential, all of the top six best fitting distributions yield hazard rates that increase initially and then decrease over time, which is consistent with the empirical hazards. For all of the top six distributions, the hazard for IsaPd is projected to be lower than that for Pd throughout the trial follow-up.

Figure 4: Hazard rates for parametric survival distributions fit to PFS on treatment for the 4th line population from ICARIA-MM, by randomised treatment



Abbreviations: IsaPd; isatuximab with pomalidomide and dexamethasone; Pd, pomalidomide with dexamethasone; PFS, progression-free survival; R, restricted; RCS, restricted cubic spline; U, unrestricted.

RSMT for PFS on treatment to end of trial follow-up and 15 years are shown in Table 2. Projected RMST for PFS on treatment after 15 years with Pd ranges from 9.3 (exponential) to 24.0 months (unrestricted Gompertz) and for IsaPd ranges from 13.6 (unrestricted Weibull) to 29.5 months (unrestricted generalised gamma). The difference in RMST for IsaPd versus Pd in PFS through 15 years ranges from -9.3 (unrestricted Gompertz) to 14.3 months (unrestricted generalised gamma). The restricted lognormal distribution yields predicted RMST for Pd, IsaPd, and the difference between IsaPd and Pd that are in the middle of the ranges of estimates from the various distributions considered.

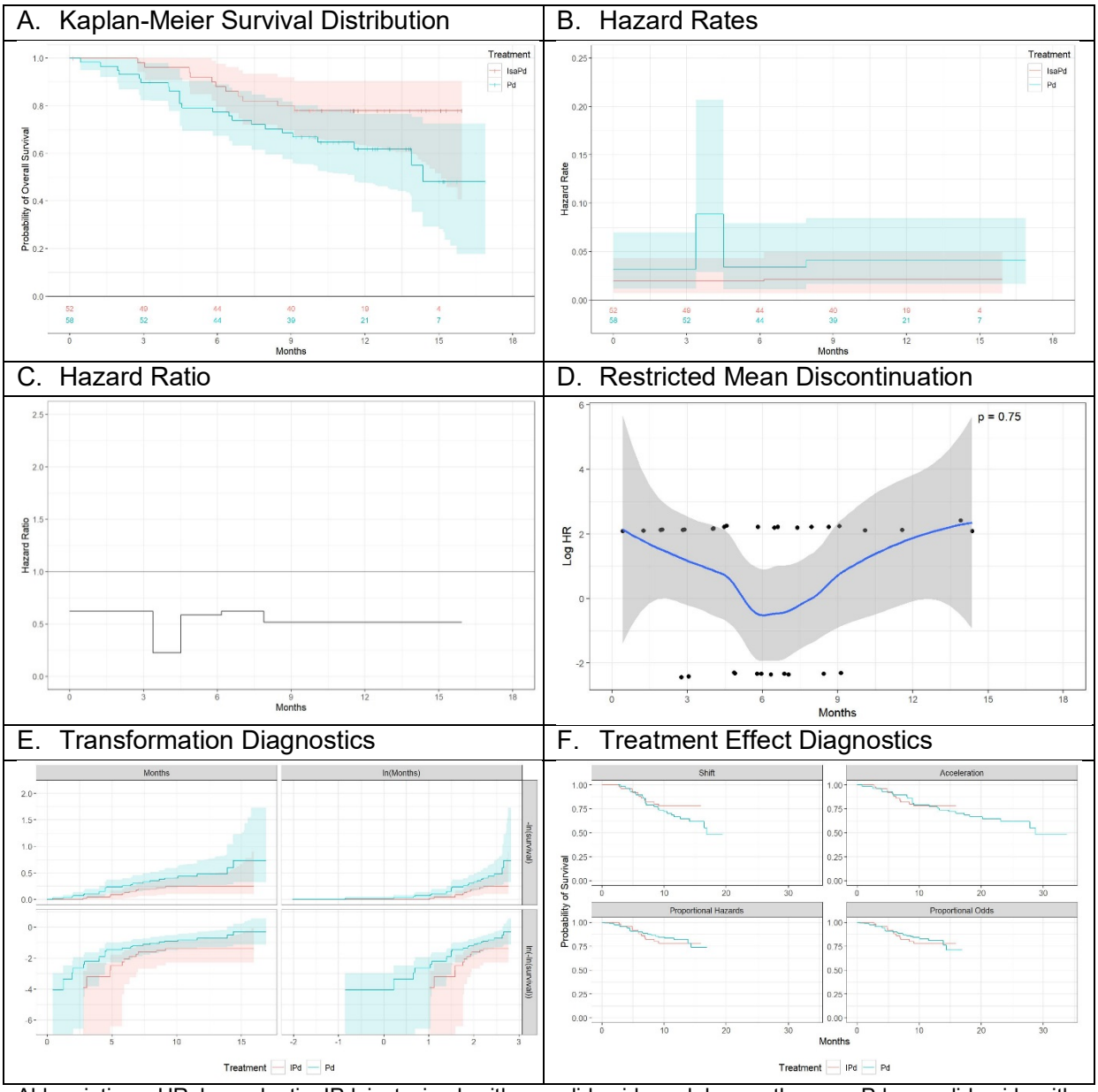
Table 2: RMST for PFS on treatment to End of Trial follow-up and 15 years among the 4th line population of ICARIA-MM, by randomised treatment arm

Distribution	End of Trial follow-up			15 years		
	IsaPd	Pd	Difference	IsaPd	Pd	Difference
Kaplan-Meier	9.3	7.4	1.9			
Exponential	9.6	7.6	2.0	14.5	9.3	5.2
Gen. F (R)	9.7	7.4	2.3	25.9	16.0	9.9
Gen. Gamma (R)	9.7	7.4	2.3	25.9	16.0	9.9
Gen. Gamma (U)	9.5	7.5	2.0	29.5	15.2	14.3
Gompertz (R)	9.5	7.6	1.9	28.3	14.2	14.1
Gompertz (U)	9.6	7.5	2.1	14.7	24.0	-9.3
Log-Logistic (R)	9.3	7.4	1.9	22.7	14.7	8.0
Log-Logistic (U)	9.6	7.4	2.2	21.2	15.4	5.8
Lognormal (R)	9.5	7.5	2.0	22.4	13.5	8.9
Lognormal (U)	9.6	7.4	2.2	20.3	14.4	5.9
RCS Log-Logistic (R)	9.6	7.5	2.1	27.3	17.4	9.9
RCS Log-Logistic (U)	9.6	7.5	2.1	28.7	17.7	11.0
RCS Lognormal (R)	9.6	7.5	2.1	24.2	14.4	9.8
RCS Lognormal (U)	9.7	7.4	2.3	25.3	14.8	10.5
RCS Weibull (R)	9.5	7.5	2.0	19.8	11.3	8.5
RCS Weibull (U)	9.5	7.5	2.0	19.0	12.0	7.0
Weibull (R)	9.6	7.5	2.1	14.6	9.4	5.2
Weibull (U)	9.6	7.6	2.0	13.6	9.8	3.8
Min	9.3	7.4	1.9	13.6	9.3	-9.3
Max	9.7	7.6	2.3	29.5	24.0	14.3

Abbreviation: PFS, progression-free survival; RMST, restricted mean survival time.

B.3 Overall survival

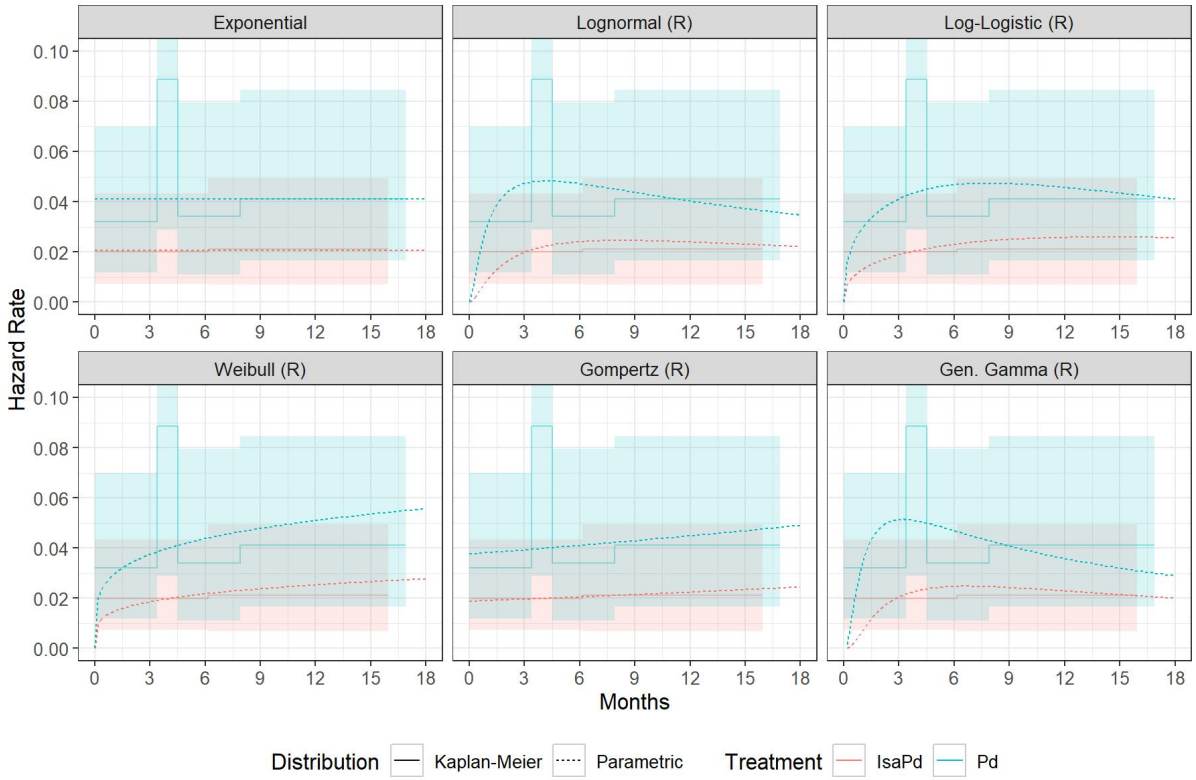
Figure 5: Overall survival for the 4th line population of ICARIA-MM, by randomised treatment



Abbreviations: HR, hazard ratio; IPd; isatuximab with pomalidomide and dexamethasone; Pd, pomalidomide with dexamethasone.

Hazard rates during the trial follow-up for the top six best fitting parametric survival distributions based on BIC for OS are compared with non-parametric hazards in Figure 6. The restricted Weibull and restricted Gompertz have increasing hazards and the exponential has constant hazards. These latter are all generally consistent with the non-parametric hazards. The restricted lognormal, restricted log-logistic and restricted generalised gamma all have hazards that are decreasing for both arms after the maximum follow-up in the trial, which is generally inconsistent with the non-parametric hazards.

Figure 6: Hazard rates for parametric survival distributions fit to OS for the 4th line population from ICARIA-MM, by randomised treatment



Abbreviations: IsaPd; isatuximab with pomalidomide and dexamethasone; OS, overall survival; Pd, pomalidomide with dexamethasone; R, restricted; U, unrestricted.

RSMT for OS to end of trial follow-up and 15 years are shown in Table 3. Projected RMST for OS after 15 years with Pd ranges from 19.7 (unrestricted Gompertz) to 70.4 (restricted generalised F) months and for IsaPd ranges from 30.1 (unrestricted Weibull) to 143.3 months (unrestricted RCS Weibull). The difference in projected RMST for OS after 15 years with IsaPd versus Pd ranges from 0.5 months (unrestricted generalised gamma) to 117.2 months (unrestricted RCS Weibull). The exponential distribution yields projections of RMST for Pd (24.4 months), IsaPd (47.3 months), and the difference between IsaPd and Pd (22.9 months) that are in the middle of ranges for all the distributions.

Table 3: RMST for OS to End of Trial follow-up and 15 years among the 4L population of ICARIA-MM, by randomised treatment arm

	End of Trial follow-up			15 years		
Distribution	**IsaPd**	**Pd**	**Difference**	**IsaPd**	**Pd**	**Difference**
Kaplan-Meier	13.6	11.5	2.1			
Exponential	13.6	11.7	1.9	47.3	24.4	22.9
Gen. F (R)	13.3	12.1	1.2	79.3	70.4	8.9
Gen. Gamma (R)	13.8	11.7	2.1	63.9	41.9	22.0
Gen. Gamma (U)	13.7	11.8	1.9	31.9	31.4	0.5
Gompertz (R)	13.6	11.7	1.9	34.2	20.3	13.9
Gompertz (U)	13.6	11.8	1.8	40.0	19.7	20.3
Log-Logistic (R)	13.6	11.5	2.1	49.1	31.1	18.0
Log-Logistic (U)	13.7	11.8	1.9	43.9	32.6	11.3
Lognormal (R)	13.7	11.8	1.9	55.4	33.8	21.6
Lognormal (U)	13.7	11.7	2.0	48.0	35.8	12.2
RCS Log-Logistic (R)	13.7	11.8	1.9	65.8	41.5	24.3
RCS Log-Logistic (U)	13.7	11.8	1.9	139.7	37.4	102.3
RCS Lognormal (R)	13.7	11.8	1.9	60.2	36.6	23.6
RCS Lognormal (U)	13.7	11.7	2.0	125.8	34.1	91.7
RCS Weibull (R)	13.7	11.8	1.9	59.6	29.7	29.9
RCS Weibull (U)	13.6	11.8	1.8	143.3	26.1	117.2
Weibull (R)	13.7	11.8	1.9	35.1	19.8	15.3
Weibull (U)	13.7	11.8	1.9	30.1	20.7	9.4
Min	13.3	11.7	1.2	30.1	19.7	0.5
Max	13.8	12.1	2.1	143.3	70.4	117.2

Source: Analyses of ICARIA-MM data
Abbreviation: OS, overall survival; RMST, restricted mean survival time.

B.4 Time to Discontinuation (TTD)

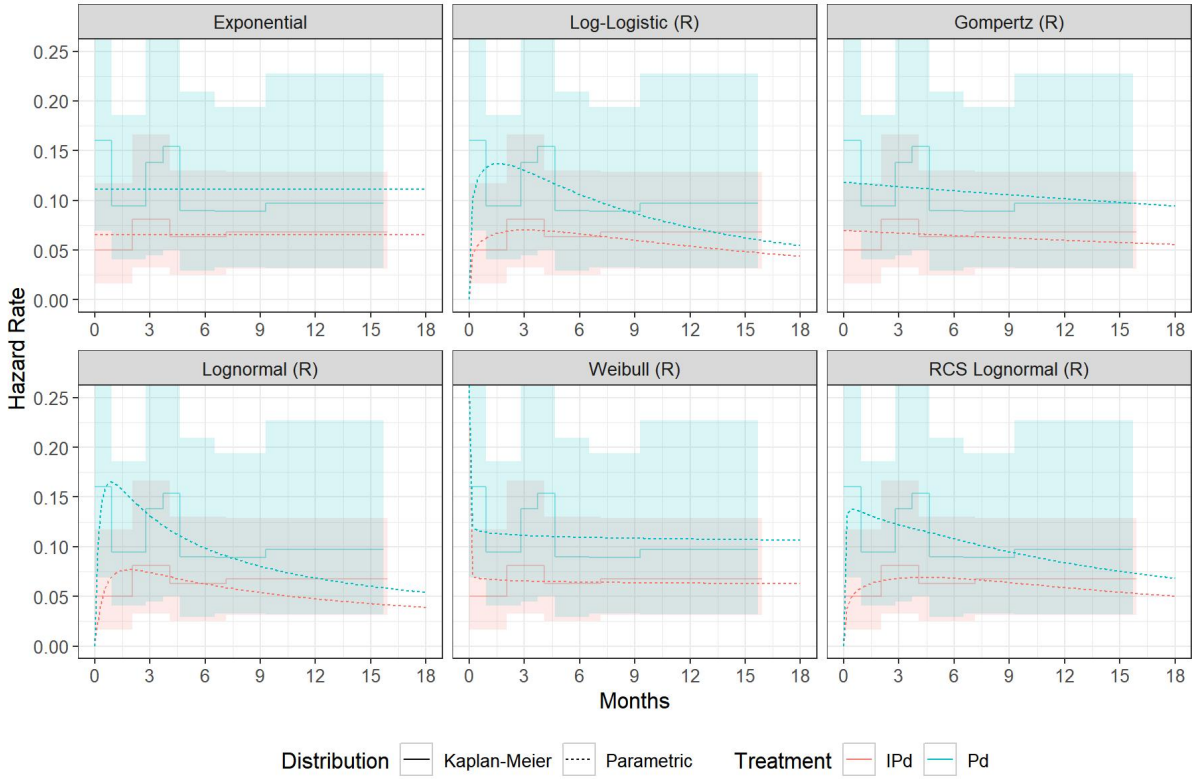
Figure 7: TTD for the 4th line population of ICARIA-MM, by randomised treatment

A. Kaplan-Meier Survival Distribution	B. Hazard Rates
Academic/commercial in confidence information removed	*Academic/commercial in confidence information removed*
C. Hazard Ratio	D. Schoenfeld Residuals
Academic/commercial in confidence information removed	*Academic/commercial in confidence information removed*
E. Transformation Diagnostics	F. Treatment Effect Diagnostics
Academic/commercial in confidence information removed	*Academic/commercial in confidence information removed*

Abbreviations: HR, hazard ratio; IPd; isatuximab with pomalidomide and dexamethasone; Pd, pomalidomide with dexamethasone; TTD, time to discontinuation.

Hazard rates during the trial follow-up for PFS for the top six best fitting parametric survival distributions are compared with non-parametric hazards in Figure 8. Some of the top six best fitting distributions yield hazard rates that increase initially and then decrease over time, while others show constant hazards over time. For all of the top six distributions, the hazard for IsaPd is projected to be lower than that for Pd throughout the trial follow-up.

Figure 8: Hazard rates for parametric survival distributions fit to TTD for the 4th line population from ICARIA-MM, by randomised treatment



Abbreviations: IPd; isatuximab with pomalidomide and dexamethasone; Pd, pomalidomide with dexamethasone; R, restricted; RCS, restricted cubic spline; TTD, time to discontinuation.

RSMT to end of trial follow-up and 15 years for TTD are shown in Table 4. Projected RMST for TTD after 15 years with Pd ranges from *Academic/commercial in confidence information removed* months (exponential) to *Academic/commercial in confidence information removed* months (unrestricted Gompertz) and for IsaPd ranges from *Academic/commercial in confidence information removed* months (unrestricted Gompertz) to *Academic/commercial in confidence information removed* months (restricted lognormal). The projected difference in RMST for IsaPd versus Pd in TTD through 15 years ranges from *Academic/commercial in confidence information removed* months (unrestricted Gompertz) to *Academic/commercial in confidence information removed* months (restricted lognormal).

Table 4: RMST for TTD to End of Trial follow-up among the 4th line population of ICARIA-MM, by randomised treatment arm

Distribution	End of Trial Follow-up			15 Years		
	IsaPd	Pd	Difference	IsaPd	Pd	Difference
Kaplan-Meier	*Academic/commercial in confidence information removed*					
Exponential						
Gen. F (R)						
Gen. Gamma (R)						
Gen. Gamma (U)						
Gompertz (R)						
Gompertz (U)						
Log-Logistic (R)						
Log-Logistic (U)						
Lognormal (R)						
Lognormal (U)						
RCS Log-Logistic (R)						
RCS Log-Logistic (U)						
RCS Lognormal (R)						
RCS Lognormal (U)						
RCS Weibull (R)						
RCS Weibull (U)						
Weibull (R)						
Weibull (U)						
Min						
Max						

Abbreviation: RMST, restricted mean survival time, TTD, time to discontinuation.

Figure 9: Quantile plots of progression-free survival for KM curves vs parametric survival distributions

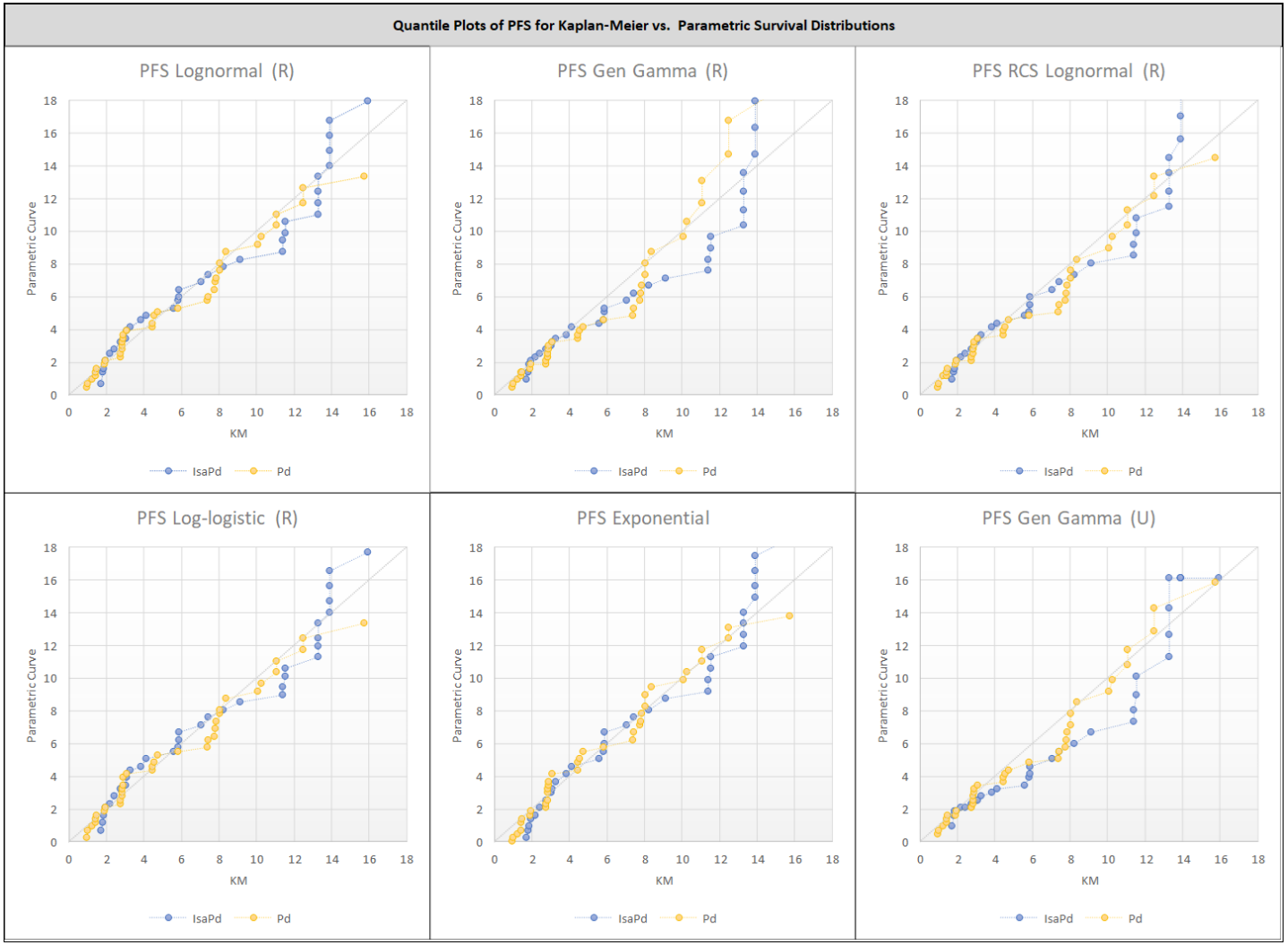
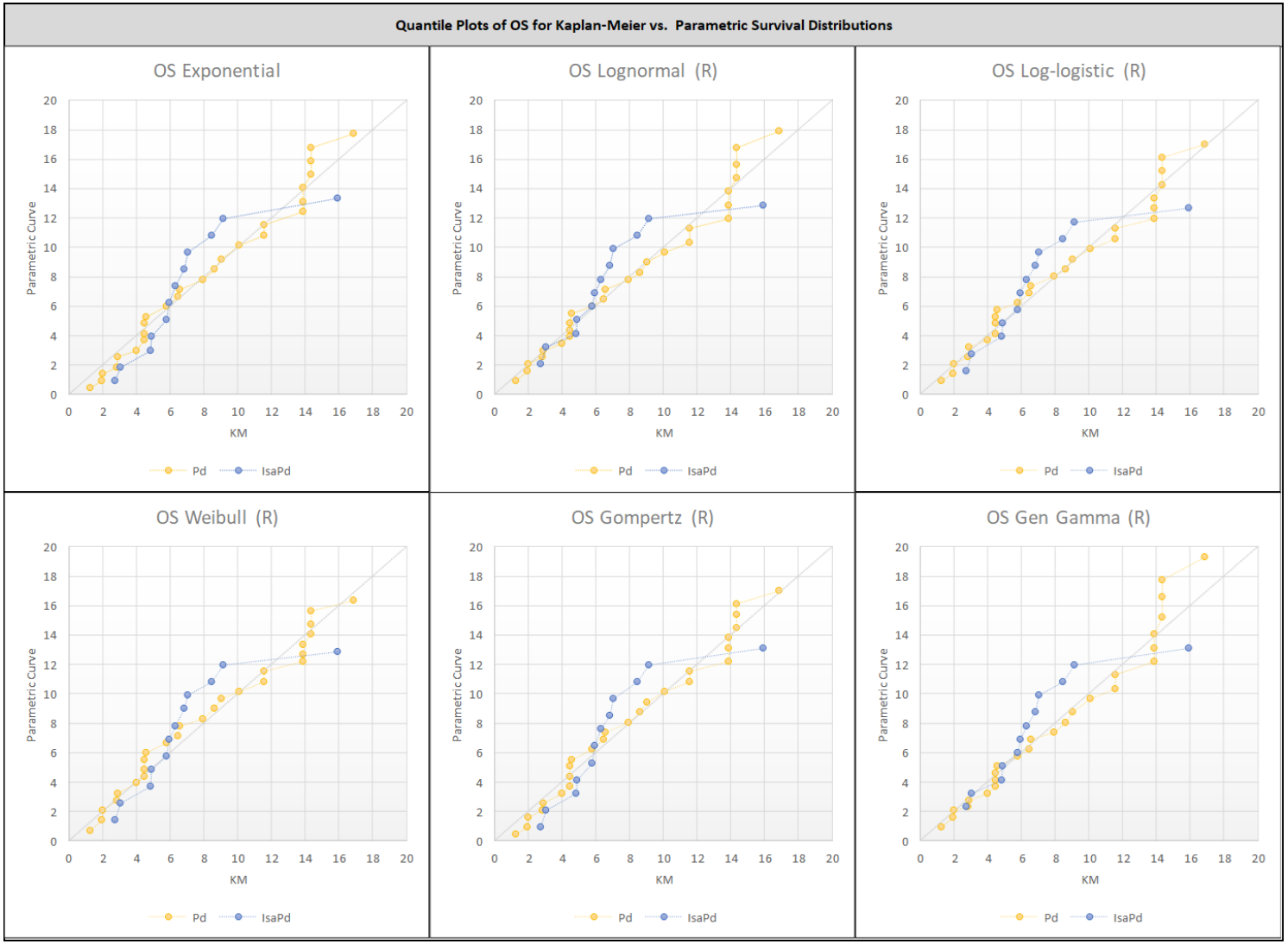


Figure 10: Quantile plots of Overall survival for KM curves vs parametric survival distributions



Appendix C. Cost-effectiveness results for IsaPd vs PanVd

Table 5: Sensitivity analyses for OS, IsaPd (at *Academic/commercial in confidence information removed* discount) vs PanVd (at list price)

Option	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	ICER (£/QALY) (deterministic)
Sanofi updated base case (OS & TTD: Exponential; PFS: Lognormal (R))							
IsaPd	*Academic/commercial in confidence information removed*			1.181	0.876	162,051	**184,899**
PanVd				-	-	-	**-**
Sensitivity analysis 1a: Use of a jointly-fitted lognormal (R) model for OS							
IsaPd	*Academic/commercial in confidence information removed*			1.575	1.119	162,836	**145,497**
PanVd				-	-	-	-
Sensitivity analysis 1b: Use of a jointly-fitted Weibull (R) model for OS							
IsaPd	*Academic/commercial in confidence information removed*			0.789	0.633	161,271	**254,685**
PanVd				-	-	-	-
Sensitivity analysis 2a: Use of a jointly-fitted log-logistic (R) model for OS							
IsaPd	*Academic/commercial in confidence information removed*			1.419	1.023	162,524	**158,879**
PanVd				-	-	-	-
Sensitivity analysis 2b: Use of a jointly-fitted RSC Weibull (R) model for OS							
IsaPd	*Academic/commercial in confidence information removed*			1.568	1.114	162,821	**146,096**
PanVd				-	-	-	-
Sensitivity analysis 2c: Use of a jointly-fitted Gen Gamma (R) model for OS							
IsaPd	*Academic/commercial in confidence information removed*			1.830	1.275	163,343	**128,075**
PanVd				-	-	-	-

Table 6: Sensitivity analyses for PFS IsaPd (at *Academic/commercial in confidence information removed* discount) vs PanVd (at list price)

Option	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	ICER (£/QALY) (deterministic)
Sensitivity analysis 3a: Use of an exponential model for PFS							
IsaPd	*Academic/commercial in confidence information removed*			1.181	0.853	162,051	**190,061**
PanVd				-	-	-	-
Sensitivity analysis 3b: Use of a jointly-fitted Weibull (R) model for PFS							
IsaPd	*Academic/commercial in confidence information removed*			1.181	0.834	162,051	**194,419**
PanVd				-	-	-	-
Sensitivity analysis 3c: Use of a jointly-fitted RCS Weibull (R) model for PFS							
IsaPd	*Academic/commercial in confidence information removed*			1.181	0.887	162,051	**182,781**
PanVd				-	-	-	-

Table 7: Sensitivity analyses for TTD, IsaPd (at *Academic/commercial in confidence information removed* discount) vs PanVd (at list price)

Option	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	ICER (£/QALY) (deterministic)
Sensitivity analysis 1: Use of a jointly-fitted log-logistic (R) model for TTD							
IsaPd	*Academic/commercial in confidence information removed*			1.181	0.876	284,781	**324,932**
PanVd				-	-	-	-
Sensitivity analysis 2: Use of a jointly-fitted Gompertz (R) for TTD							
IsaPd	*Academic/commercial in confidence information removed*			1.181	0.876	203,620	**232,328**
PanVd				-	-	-	-
Sensitivity analysis 3: Use of a jointly-fitted lognormal (R) model for TTD							
IsaPd	*Academic/commercial in confidence information removed*			1.181	0.876	300,212	**342,537**
PanVd				-	-	-	-
Sensitivity analysis 4: Use of a jointly-fitted Weibull (R) model for TTD							
IsaPd	*Academic/commercial in confidence information removed*			1.181	0.876	166,812	**190,330**
PanVd				-	-	-	-

Table 8: Sensitivity analyses for OS, IsaPd (at *Academic/commercial in confidence information removed* discount) vs PanVd (at list price)

Option	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	ICER (£/QALY) (deterministic)
Sanofi updated base case (OS & TTD: Exponential; PFS: Lognormal (R))							
IsaPd	*Academic/commercial in confidence information removed*						
PanVd							
Sensitivity analysis 1a: Use of a jointly-fitted lognormal (R) model for OS							
IsaPd	*Academic/commercial in confidence information removed*						
PanVd							
Sensitivity analysis 1b: Use of a jointly-fitted Weibull (R) model for OS							
IsaPd	*Academic/commercial in confidence information removed*						
PanVd							
Sensitivity analysis 2a: Use of a jointly-fitted log-logistic (R) model for OS							
IsaPd	*Academic/commercial in confidence information removed*						
PanVd							
Sensitivity analysis 2b: Use of a jointly-fitted RSC Weibull (R) model for OS							
IsaPd	*Academic/commercial in confidence information removed*						
PanVd							
Sensitivity analysis 2c: Use of a jointly-fitted Gen Gamma (R) model for OS							
IsaPd	*Academic/commercial in confidence information removed*						
PanVd							

Table 9: Sensitivity analyses for PFS IsaPd (at *Academic/commercial in confidence information removed* discount) vs PanVd (at list price)

Option	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	ICER (£/QALY) (deterministic)
Sensitivity analysis 3a: Use of an exponential model for PFS							
IsaPd	*Academic/commercial in confidence information removed*						
PanVd							
Sensitivity analysis 3b: Use of a jointly-fitted Weibull (R) model for PFS							
IsaPd	*Academic/commercial in confidence information removed*						
PanVd							
Sensitivity analysis 3c: Use of a jointly-fitted RCS Weibull (R) model for PFS							
IsaPd	*Academic/commercial in confidence information removed*						
PanVd							

Table 10: Sensitivity analyses for TTD, IsaPd (at *Academic/commercial in confidence information removed* discount) vs PanVd (at list price)

Option	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	ICER (£/QALY) (deterministic)
Sensitivity analysis 1: Use of a jointly-fitted log-logistic (R) model for TTD							
IsaPd	*Academic/commercial in confidence information removed*						
PanVd							
Sensitivity analysis 2: Use of a jointly-fitted Gompertz (R) for TTD							
IsaPd	*Academic/commercial in confidence information removed*						
PanVd							
Sensitivity analysis 3: Use of a jointly-fitted lognormal (R) model for TTD							
IsaPd	*Academic/commercial in confidence information removed*						
PanVd							
Sensitivity analysis 4: Use of a jointly-fitted Weibull (R) model for TTD							
IsaPd	*Academic/commercial in confidence information removed*						
PanVd							

C.1 Impact of adjusting for subsequent treatments on comparison of IsaPd vs PanVd

In a scenario analysis where post study treatments based on expert opinion (see below) are used instead of those used in the ICARIA-MM trial, ICER for IsaPd vs PanVd is £167,524

Table 11: Proportion of patients receiving subsequent anti-cancer treatments after IsaPd and PanVd from UK clinical expert opinion

Subsequent anti-cancer treatment	Treatment arm	
	IsaPd	PanVd
Bendamustine	13.31%	13.33%
Bortezomib	25.23%	5.00%
Carfilzomib	0.00%	0.00%
Daratumumab	0.00%	14.17%
Etoposide	3.13%	0.00%
Thalidomide	20.00%	20.00%
Lenalidomide	0.00%	0.00%
Melphalan	11.78%	5.00%
Panobinostat	17.82%	0.00%
Pomalidomide	0.00%	30.00%

C.2 Adjustment for post study use of daratumumab and lenalidomide

In a scenario analysis where post study treatment with daratumumab is adjusted using IPCW methods, the ICER for IsaPd vs PanVd is *Academic/commercial in confidence information removed*.

In a scenario analysis where post study treatment with daratumumab and lenalidomide is adjusted using IPCW methods, the ICER for IsaPd vs PanVd is *Academic/commercial in confidence information removed.*

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Technical engagement response form

Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [ID1477]

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We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **Thursday 9 April 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise,

all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Dr Neil Rabin**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Consultant Haematologist, University College London Hospitals and North Middlesex University Hospital.** **Clinical Expert, nominated by Sanofi**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**HONARARIA: Celgene, Janssen, Takeda.** **CONSULTING/ADVISORY ROLE – Celgene, Takeda, Amgen, Karyopharm.**

Questions for engagement

Issue 1: Treatment pathway and post-hoc subgroup analyses	
1. Where would ISA/POM/DEX likely be used in NHS clinical practice? Is 4th line the only relevant position for the committee to consider in their decision making?	**There is an unmet need for patients with relapsed / refractory Myeloma. ISA/POM/DEX helps address this issue and is an important treatment. These patients have received lenalidomide and a proteasome inhibitor, and would have met the eligibility criteria for the ICARIA-MM trial.** **ISA/POM/DEX is appropriate at 4th line therapy for the majority of patients. Bortezomib is given for patients that are newly diagnosed (TA311) and at first relapse in combination with Daratumumab (CDF) at 2nd Line. Patients would then receive Ixazomib Lenaldiomide and Dexamethasone (CDF) at 3rd line.** **A group of patients who are not transplant eligible may receive Lenalidomide upfront (TA587) or at 2nd line (TA586). Assuming Bortezomib has been given during their treatment pathway, then ISA/POM/DEX could be given at 3rd line for a minority of patients.** **ISA/POM/DEX would replace POM/DEX (TA427) at 4th line in the current treatment pathway. It would also naturally replace Daratumumab monotherapy at 4th line (CDF), as it is likely to have far superior clinical outcomes.** **There are likely to be limited treatment options at 5th line if patients were to receive ISA/POM/DEX at 4th line given the current availability of therapies.**
2. Are the post-hoc subgroup analyses from the ICARIA-MM trial used in the economic modelling robust and appropriate for decision making?	**Post-hoc subgroup analyses from the ICARIA-MM trial used for economic modelling is appropriate. Baseline characteristics appear to be similar in both treatment groups. Importantly, patients were randomly assigned to POM/DEX +/- ISA at trial entry reducing bias in patient selection. The results reported for 4th line patients are as expected based on the reported data.**

Issue 2: ICARIA-MM clinical trial	
3. Does using an anti-CD38 monoclonal antibody once have an impact of the effect of using another anti-CD38 monoclonal antibody later in the treatment pathway?	**ICARIA-MM trial excluded patients that were refractory to an anti-CD38 monoclonal antibody. Prior exposure to an anti-CD38 monoclonal antibody was allowed. It would therefore be appropriate to exclude patients that were refractory to an anti-CD38 monoclonal antibody, and include those that had prior exposure without demonstrating refractoriness to this agent.** **In current clinical practice patients will receive Daratumumab Bortezomib Dexamethasone (CDF) at 2nd Line. A small group of patients may have received an anti-CD38 monoclonal antibody as part of a clinical trial. These patients should be eligible to receive ISA/POMA/DEX so long as they are not refractory to a previous anti-CD38 monoclonal antibody. Anti-CD38 monoclonal antibodies work best when partnered with an IMiD. It is therefore expected that these patients are likely to gain significant clinical benefit.** **There is no reason to specify a non-anti-CD38-based treatment between these anti-CD38 monoclonal antibody therapies, as has been stated in the Technical report.**
Issue 3: Relevant comparators	
4. What treatments are considered established clinical practice at 4th line and are therefore relevant comparators for ISA/POM/DEX?	**POM/DEX(TA427) is the appropriate comparator at 4th line.** **Patients receiving POM/DEX would have received at least 2 prior treatments including lenalidomide and a proteasome inhibitor. Importantly POM/DEX is the control arm of the ICARIA-MM trial.** **In current practice patients receive Daratumumab monotherapy at 4th line (CDF), as it can only be given at this line. Daratumumab monotherapy is only available on the CDF and has been excluded for analysis in this appraisal.** **Prior to Daratumumab monotherapy being available in April 2018, POM/DEX was given as standard of care at 4th line in routine clinical practice. This emphasises the importance of**

	POM/DEX as the appropriate comparator for ISA/POM/DEX. **There are no other comparators at 4th line, other than palliative chemotherapy/care. PANO/BORT/DEX would either be given 5th line and beyond, or at 3rd line for a small subset of patients with a good performance status and having demonstrated a durable response to prior Bortezomib.**
5. Is PANO/BORT/DEX a relevant comparator?	**PANO/BORT/DEX is not an appropriate comparator at 4th line. In current practice most patients would receive either Daratumumab monotherapy (CDF) or POM/DEX(TA427). This is because both of these therapies are well tolerated with improved outcomes for patients.** **PANO/BORTDEX is currently used at 5th line and beyond for patients who have exhausted all current therapies. Whilst it could be used at 4th line it is not the best therapy for patients due to lack of response and toxicity. As mentioned before a small group of patients may receive PANO/BORT/DEX at 3rd line if they have a good performance status, and have received both Lenalidomide and Bortezomib, and importantly are not refractory to Bortezomib.**
Issue 4: Matched-adjusted indirect comparison	
6. Is the company's matched adjusted indirect comparison (MAIC) between ISA/POM/DEX and PANO/BORT/DEX valid?	**Unable to comment on this.**
Issue 5: Subsequent treatments	
7. What treatments are commonly used as a 5th line therapy in NHS clinical practice (not considering current CDF recommended drugs)?	**There is no uniform treatment for patients at 5th line and beyond. Choice of therapy would depend upon:** **1. Response to prior therapies and whether refractory to a proteasome inhibitor or immunomodulatory agent (IMiD)** **2. Bone marrow reserve (anaemia, neutropaenia, thrombocytopaenia), and need for**

	blood product support **3. Performance status and co-morbidities (bone disease, renal function, or pre-existing)** **4. Whether treatment is delivered at home or in hospital.** **Unfortunately patients at 5th line have a poor outcome. Assuming patients are being actively being treated (rather than receiving palliation alone) treatments in the UK would include: thalidomide, cyclophosphamide, PANO/BORT/DEX or steroids alone.** **Given that most patients are receiving Daratumumab monotherapy (CDF) at 4th line, POM/DEX(TA427) would currently be the therapy most often given at 5th line currently. As mentioned previously POM/DEX would be naturally given at 4th line if Daratumumab monotherapy (CDF) was not available.**
8. Do the subsequent treatments permitted in the ICARIA-MM trial impact on the generalisability of the overall survival data to clinical practice in the NHS?	**As there is no uniform treatment beyond 5th line in the UK or internationally, the results reported in the ICARIA-MM trial are likely to be generalisable. The response rate to any of the reported therapies is likely to be less than 30% (and more likely around 20%). As stated in the Technical report Lenalidomide and Daratumumab are likely to be unavailable in UK practice outside of a clinical trial. Other named therapies maybe available to some patients.**
Issue 6: Extrapolation of overall survival, progression-free survival and time to treatment discontinuation	
9. How robust is the extrapolation of overall survival, progression-free survival and time to treatment discontinuation?	**Whilst it is true that patients beyond 5th line have a very poor survival, there will be a small subgroup that maybe alive at 10 years (<10%). This would depend upon response to prior therapies and importantly having a very long treatment free interval between each of these therapies.**
10. How informative is the ERG's sensitivity analysis regarding the extrapolation of overall survival, progression-free survival and time to treatment	**Overall survival is the most important clinical outcome, alongside quality of life data. Given that the data is immature at this time and further trial analysis is awaited, extrapolated OS, PFS and Treatment discontinuation methods are important. I am not able**

discontinuation?	**to comment on the methods used by the ERG.**
Issue 7: Time horizon	
11. Over what time horizon would you expect all differences in benefits and costs that arise as a consequence of treatment choice to materialise?	**There will be a small number of patients that will be alive beyond 15 years.**
Issue 8: Cost uncertainties in the analysis	
12. Do the differences in the relative dose intensities in the ISA/POM/DEX and POM/DEX arms of the ICARIA-MM trial impact on the robustness of the cost-effectiveness estimates?	**Unable to comment**
13. Is the assumption of no drug wastage reasonable?	**Unable to comment**
14. Are the costs of treatment underestimated in the company model?	**Unable to comment**
Issue 9: Health utility values	
15. Are the utility values included in the company model appropriate?	**Unable to comment**
Issue 10: Cancer Drugs Fund	
16. Is there further data being collected that could reduce uncertainty surrounding longer-term effectiveness and health outcomes in the relevant population(s)?	**Further data is being collected which should reduce the uncertainty surrounding the long-term effectiveness and health outcomes.**
17. When will these additional data become available?	**Expected in 2021**

18. How suitable is the technology for use in the Cancer Drugs Fund (CDF)?	**There is clearly an unmet clinical need for patients with relapsed / refractory myeloma. POMA/ISA/DEX would fit naturally into the treatment algorithm at 4th line (see answer to Question 1). If POMA/ISA/DEX is not considered for baseline commissioning then it would be an appropriate treatment offered by the CDF. Data for the CDF could be collected from the SACT database (number of cycles delivered, dose modifications) and/or bespoke data collection. This could be collected whilst more mature data is published from the ICARIA-MM trial.**
Issue 11: End of Life	
19. Under standard care, is the life expectancy of adults with relapsed or refractory multiple myeloma after 3 prior treatments less than 24 months?	**There is published data that supports an overall survival of less than 2 years for patients with relapsed/refractory multiple myeloma. In a multicentre study, patients who have received at least prior lines of therapy, are refractory to both an IMiD (lenalidomide or pomalidomide) and a PI (bortezomib or carfilzomib), and have been exposed to an alkylating agent the overall survival was 13 months; 95% CI 11 to 15 months (Kumar et al *Leukaemia* 2017 Nov, 31 (11):2443-2448). This patient cohort would be similar to those recruited in the ICARIA-MM trial. Previously published data supports this as well.** **Clinical experience in the UK is consistent with this as well. Life expectancy for patients with or refractory myeloma after 3 prior treatments in less than 24 months. This would therefore meet the end of life criteria.**
20. Does ISA/POM/DEX extend life for more than 3 months compared with standard care for adults with relapsed or refractory multiple myeloma after 3 prior treatments?	**It is expected and clinically reasonable for ISA/POM/DEX to extend life by more than 3 months compared with the standard of care (POM/DEX). Note the standard of care at 4th line in the UK is POM/DEX(TA427), which is the control arm on the ICARIA-MM trial.**

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- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise,

all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Stakeholder
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Questions for engagement

Issue 1: Treatment pathway and post-hoc subgroup analyses	
1. Where would ISA/POM/DEX likely be used in NHS clinical practice? Is 4th line the only relevant position for the committee to consider in their decision making?	Support use of Isa/pom/dex in 4th line setting. While this is a transitional issue, there is currently also unmet need for the relatively small number of myeloma patients at fifth line and beyond whose treatment options are limited. We would therefore ask whether options can be explored to enable isa/pom/dex to also be available to patients beyond fourth line.
2. Are the post-hoc subgroup analyses from the ICARIA-MM trial used in the economic modelling robust and appropriate for decision making?	No comment
Issue 2: ICARIA-MM clinical trial	
3. Does using an anti-CD38 monoclonal antibody once have an impact of the effect of using another anti-CD38 monoclonal antibody later in the treatment pathway?	The ICARIA trial excluded patients who were refractory to an anti-CD38 monoclonal antibody, but did not exclude patients with previous exposure. There is also evidence that synergistic effects between IMiDs and daratumumab potentially overcome refractoriness to both anti-myeloma agents. [i] Patients who have been exposed but are not refractory to daratumumab should be able to access isatuximab, pomalidomide and dexamethasone, line with ICARIA inclusion criteria.
Issue 3: Relevant comparators	
4. What treatments are considered established clinical practice at 4th line and are therefore	Pomalidomide and dexamethasone is the appropriate comparator.

relevant comparators for ISA/POM/DEX?	(Daratumumab monotherapy is also used at fourth line but is not treated as a comparator since it is approved via the Cancer Drugs Fund (CDF)) While approved for use at this point in the pathway, panobinostat is reserved for later treatment lines given its toxicity. Our view therefore is that for panobinostat established clinical practice is to use it later than fourth line.
5. Is PANO/BORT/DEX a relevant comparator?	No. (See above)
Issue 4: Matched-adjusted indirect comparison	
6. Is the company's matched adjusted indirect comparison (MAIC) between ISA/POM/DEX and PANO/BORT/DEX valid?	No comment
Issue 5: Subsequent treatments	
7. What treatments are commonly used as a 5th line therapy in NHS clinical practice (not considering current CDF recommended drugs)?	Pomalidomide and dexamethasone, panobinostat, bortezomib and dexamethasone, bendamustine.
8. Do the subsequent treatments permitted in the ICARIA-MM trial impact on the generalisability of the overall survival data to clinical practice in the NHS?	It is difficult to comment with certainty on the impact of subsequent treatments to overall survival data. For isatuximab, pomalidomide and dexamethasone, it is reasonable to interpret that the trend towards overall survival improvement will continue. There should be an opportunity for the data to confirm this to be collected via a mechanism such as the CDF. It is noted that subsequent treatments permitted in the trial are not routinely used on the NHS. The myeloma treatment pathway is increasingly complex and sequencing impact will become ever more difficult to meaningfully assess. We need a "fit for purpose" approach to the weight given to the possible impact of subsequent treatments.

Issue 6: Extrapolation of overall survival, progression-free survival and time to treatment discontinuation	
9. How robust is the extrapolation of overall survival, progression-free survival and time to treatment discontinuation?	See below.
10. How informative is the ERG's sensitivity analysis regarding the extrapolation of overall survival, progression-free survival and time to treatment discontinuation?	We emphasise the clear clinical benefit delivered in ICARIA's to PFS and ORR. Overall survival is clearly very important to patients and their families and it is right that treatments are scrutinised on their ability to deliver this. However, it is increasingly difficult to reach a median OS in myeloma trials. Managed access mechanisms such as the CDF should be used to deliver access while securing better OS data.
Issue 7: Time horizon	
11. Over what time horizon would you expect all differences in benefits and costs that arise as a consequence of treatment choice to materialise?	No comment.
Issue 8: Cost uncertainties in the analysis	
12. Do the differences in the relative dose intensities in the ISA/POM/DEX and POM/DEX arms of the ICARIA-MM trial impact on the robustness of the cost-effectiveness estimates?	No comment.
13. Is the assumption of no drug wastage reasonable?	No comment
14. Are the costs of treatment underestimated in the company model?	No comment
Issue 9: Health utility values	

15. Are the utility values included in the company model appropriate?	No comment.
Issue 10: Cancer Drugs Fund	
16. Is there further data being collected that could reduce uncertainty surrounding longer-term effectiveness and health outcomes in the relevant population(s)?	See below
17. When will these additional data become available?	See below
18. How suitable is the technology for use in the Cancer Drugs Fund (CDF)?	This is difficult to assess in terms of cost effectiveness due to the commercial in confidence nature of commercial negotiations. That aside, we view isa/pom/dex as exactly the kind of treatment which is a candidate for the CDF. The CDF was designed to deliver access to the most promising cancer drugs, to drive value for money and to help resolve HTA challenges arising from clinical uncertainty. Isa/pom/dex delivers clear and significant clinical benefit, in the form of a novel triplet MAB/IMiD triplet not currently available. We accept that OS data is immature. Collecting further data would enable a clearer picture of the treatment's value to emerge. We encourage the company, NICE and NHSE to do everything possible to ensure that isa/pom/dex is a CDF candidate.
Issue 11: End of Life	
19. Under standard care, is the life expectancy of adults with relapsed or refractory multiple myeloma after 3 prior treatments less than 24 months?	Yes. Data has shown that the life expectancy for multiply relapsed myeloma patients with prior treatment with a PI and an IMiD is typically less than 12 months. For patients who are refractory to both a PI and an IMid, median life expectancy is 8-9 months, and for patients who are refractory to

	three or four of the common PIs and IMiDs median life expectancy decreases to only 3-5 months.[ii] We agree with the data on End of Life contained within the company's submission at B.1.3.2
20. Does ISA/POM/DEX extend life for more than 3 months compared with standard care for adults with relapsed or refractory multiple myeloma after 3 prior treatments?	Yes.

[i] CD-38 Antibodies in Mutliple Myeloma: Mechanisms of Action and Modes of Resistance https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6158369/

[ii] 6 Gooding S, Lau IJ, Sjeikh M et al, Double Relapsed and/or Refractory Multiple Myeloma: Clinical Outcomes and Real World Healthcare Costs. PLoS ONE. 2015. 10 (9): e0136207)

NICE National Institute for Health and Care Excellence

Technical engagement response form

Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [ID1477]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **Thursday 9 April 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise,

all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Janssen-Cilag Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Questions for engagement

Issue 1: Treatment pathway and post-hoc subgroup analyses	
1. Where would ISA/POM/DEX likely be used in NHS clinical practice? Is 4th line the only relevant position for the committee to consider in their decision making?	There remains unmet need at 3rd line for patients exposed and refractory to lenalidomide as the current treatment options of Rd or IxaRd (CDF) become unavailable leaving PanVd as the only treatment option which is not that well tolerated.
2. Are the post-hoc subgroup analyses from the ICARIA-MM trial used in the economic modelling robust and appropriate for decision making?	No comment
Issue 2: ICARIA-MM clinical trial	
3. Does using an anti-CD38 monoclonal antibody once have an impact of the effect of using another anti-CD38 monoclonal antibody later in the treatment pathway?	There is currently no retreatment data available for anti-CD38 monoclonal antibody therefore the effect of retreatment on clinical efficacy it not known/understood.
Issue 3: Relevant comparators	
4. What treatments are considered established clinical practice at 4th line and are therefore relevant comparators for ISA/POM/DEX?	Other than POM/DEX, daratumumab monotherapy (CDF) is used extensively in clinical practice at 4th line. Whilst daratumumab is only currently available via CDF, Janssen believe that it should be considered a relevant active comparator treatment if the CDF is also being considered for ISA/POM/DEX.
5. Is PANO/BORT/DEX a relevant comparator?	No comment

Issue 4: Matched-adjusted indirect comparison	
6. Is the company's matched adjusted indirect comparison (MAIC) between ISA/POM/DEX and PANO/BORT/DEX valid?	No comment
Issue 5: Subsequent treatments	
7. What treatments are commonly used as a 5th line therapy in NHS clinical practice (not considering current CDF recommended drugs)?	No comment
8. Do the subsequent treatments permitted in the ICARIA-MM trial impact on the generalisability of the overall survival data to clinical practice in the NHS?	No comment
Issue 6: Extrapolation of overall survival, progression-free survival and time to treatment discontinuation	
9. How robust is the extrapolation of overall survival, progression-free survival and time to treatment discontinuation?	No comment
10. How informative is the ERG's sensitivity analysis regarding the extrapolation of overall survival, progression-free survival and time to treatment discontinuation?	No comment
Issue 7: Time horizon	
11. Over what time horizon would you expect all differences in benefits and costs that arise as a consequence of treatment choice to materialise?	No comment
Issue 8: Cost uncertainties in the analysis	

12. Do the differences in the relative dose intensities in the ISA/POM/DEX and POM/DEX arms of the ICARIA-MM trial impact on the robustness of the cost-effectiveness estimates?	No comment
13. Is the assumption of no drug wastage reasonable?	Janssen understanding is that vial sharing is sporadic and not done in all sites. Patients are not always treated on the same day and, given the limited stability of the treatment once it is reconstituted, it is not often feasible to vial share to avoid wastage.
14. Are the costs of treatment underestimated in the company model?	No comment
Issue 9: Health utility values	
15. Are the utility values included in the company model appropriate?	No comment
Issue 10: Cancer Drugs Fund	
16. Is there further data being collected that could reduce uncertainty surrounding longer-term effectiveness and health outcomes in the relevant population(s)?	No comment
17. When will these additional data become available?	No comment
18. How suitable is the technology for use in the Cancer Drugs Fund (CDF)?	No comment
Issue 11: End of Life	
19. Under standard care, is the life expectancy of adults with relapsed or refractory multiple myeloma	No comment

after 3 prior treatments less than 24 months?	
20. Does ISA/POM/DEX extend life for more than 3 months compared with standard care for adults with relapsed or refractory multiple myeloma after 3 prior treatments?	It is important that the end of life criteria has already been accepted for this line of therapy before in TA 427 and TA 510 as has been highlighted by the ERG. The ERG also presents a model analysis of the predicted mean survival for Pd patients that is expected to be longer than 2 years (exact number has been black out as confidential). This may be an overestimation as Pd patients in the trial where allowed to receive Dara monotherapy as subsequent therapy which will inflate Pd survival while this is not in line with UK clinical practice.

Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma. A Single Technology Appraisal. ERG assessment of the company's response to the NICE Technical Engagement Report

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Date completed	Date completed 21/04/2020

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 12/97/72.

Declared competing interests of the authors

None of the authors has any conflicts of interest to declare.

Acknowledgements

We would also like to thank Andrea Shippam, Programme Manager, ScHARR, for providing administrative support and in preparing and formatting the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Stevenson M, Stevens J, Navega Biz A. Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma. A Single Technology Appraisal. ERG assessment of the company's response to the technical engagement report. School of Health and Related Research (ScHARR), 2020.

Contributions of authors

Matt Stevenson and Aline Navega Biz critiqued the health economic issues raised by the company. John Stevens critiqued the statistical issues raised by the company. All authors were involved in drafting and commenting on the final report.

1 Background

This document provides an assessment of the company's response to the NICE Technical Engagement Report. The Evidence Review Group (ERG) has limited the assessment to matters that are deemed factually incorrect or where the company's opinion appears to be strongly at odds to the opinion of the ERG.

The updated version of the company's model arrived the day before the deadline for the ERG report. Due to limited time, the ERG focused its efforts on verifying the changes made by the company and their impact on the results. The updated version of the model submitted by the company corresponds, in general terms, to the ERG preferred analysis.[1] The following changes were included: (i) a new method to assign medication costs, where the full cycle cost of each drug are applied at the beginning of each treatment cycle; (ii) amendment of the method of sampling probabilistic health state utilities (via a bootstrapped distribution); (iii) inclusion of two additional scenario analysis, where the overall survival (OS) is adjusted using the Inverse Probability of Censoring Weights (IPCW) method to adjust for the use of fifth-line (5L) treatments not recommended for use in England; (iv) fixing a small error in the probabilistic sampling of terminal costs; (v) updating the high/low values for terminal decrements in utility within deterministic sensitivity analyses; and (vi) an increased Patient Access Scheme (PAS) discount for isatuximab.

The company has presented an updated deterministic base case analysis, using a PAS discount of [redacted] and incorporating the changes listed above. Henceforth all ICERs will be presented in terms of cost per QALY gained and all use the list price for comparators and subsequent treatments. This analysis indicated that isatuximab in combination with pomalidomide and dexamethasone (IsaPd) generates an additional 1.10 quality-adjusted life years (QALYs) and additional costs of £113,179 compared with pomalidomide and low-dose dexamethasone (Pd). The resulting incremental cost-effectiveness ratio (ICER) for IsaPd versus Pd is estimated to be £102,745 (Table 1).

The ERG notes that all ICERs reported by the company's technical engagement response are deterministic, which the company justified '*as being the most appropriate for decision making until further data collection is performed via CDF*'. The ERG disagrees and would prefer the base case to be probabilistic as this provides a more accurate estimate of the ICER in a non-linear model. Therefore, the ERG has obtained the probabilistic results from the updated model submitted by the company (Table 1 and Table 2). The probabilistic version of the model produces a slightly higher ICER for IsaPd versus Pd, estimated to be £108,320.

Table 1: Company's new base case results - IsaPd versus Pd (based on the company's updated model, discounted values)

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
Probabilistic model – 1000 iterations							
IsaPd	[redacted]	[redacted]	[redacted]	1.741	1.131	£122,537	**£108,320**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic model							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.102	£113,179	**£102,725**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year IsaPd – isatuximab in combination with pomalidomide and dexamethasone; Pd – pomalidomide and dexamethasone

The company has also provided results for IsaPd compared to panobinostat, bortezomib and dexamethasone (PanVd); however, the company believes that PanVd should not be a comparator. The company's new base case analysis suggests that IsaPd generates an additional 0.876 QALYs at an additional cost of £162,051 compared with PanVd; the ICER for IsaPd versus PanVd is estimated to be £184,899 (Table 2). The probabilistic version of the model produces a higher ICER for IsaPd versus PanVd, estimated to be £203,006.

Table 2: Company's new base case results - IsaPd versus PanVd (based on the company's updated model, discounted values)

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
Probabilistic model – 1000 iterations							
IsaPd	[redacted]	[redacted]	[redacted]	1.159	0.859	£174,472	**£203,006**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic model							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.876	£162,051	**£184,899**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year IsaPd – isatuximab in combination with pomalidomide and dexamethasone; PanVd – panobinostat, with bortezomib and dexamethasone

[redacted]

2 The questions for engagement

NICE identified eleven questions for engagement; some of these include sub-questions. The eleven issues (as defined by the company) are considered in turn below.

2.1 Issue 1: Treatment pathway and post-hoc subgroup analyses

The company has provided new data obtained through market research that indicates that lenalidomide '*remains to be generally used at 3L (32%) via routine commissioning with dexamethasone and 51% in combination with ixazomib (via CDF)… making the 4L position for isatuximab most appropriate.*' The ERG has no comment to make on these new data.

The company undertook statistical analyses to support the use of the fourth-line (4L) data used in the model. Multivariable Cox proportional hazards models were used to assess the robustness of the effect of IsaPd versus Pd after adjusting for relevant baseline characteristics. The analyses presented included: a full model (all prognostic factors included); a reduced model (only factors considered statistically significant); and a clinically relevant model (factors considered statistically significant plus additional factors considered prognostic by clinical experts consulted by the company). Separate analyses were performed for the ITT and 4L patients. For the 4L patients, the company compared baseline characteristics between treatments using formal significance tests and commented on baseline balance. The ERG notes that baseline balance is irrelevant and the analysis should include all measured prognostic factors irrespective of baseline balance or statistical significance.

For ITT patients, the hazard ratio (HR) for the effect of IsaPd versus Pd from the clinically relevant model was [redacted]. For 4L patients, the HR for the effect of IsaPd versus Pd from the clinically relevant model was [redacted] The estimates of the treatment effects in the ITT and 4L patients were similar. However, there was considerable uncertainty in the estimate of treatment effect in 4L patients.

2.2 Issue 2: ICARIA-MM clinical trial[2]

This issue focussed on whether the use of an anti-CD38 monoclonal antibody prior to isatuximab would affect the relative efficacy of IsaPd compared with Pd, as being refractory to an anti-CD38 monoclonal antibody was an exclusion criteria in the ICARIA-MM trial.[2] The company has summarised the clinical advice to the ERG correctly in that they would use IsaPd "*in daratumumab-exposed patients provided they were not refractory to daratumumab in a prior line of therapy and had a non-anti-CD38-based treatment inbetween*".

2.3 Issue 3: Relevant comparators

This issue focussed on what interventions are currently used at 4L and what would be a comparator to IsaPd acknowledging that products in the CDF are not considered comparators under the NICE process. Clinical advice to the ERG was mixed regarding the use in 4L of PanVd, with two saying it is used and one saying that it is not. The company provided new data on the use of PanVd across time from the IPSOS Oncology Monitor with a value of 7% (n=35) in 2017, 2% (n= 161) in 2018 and 1%

(n=295) in 2019.[3] If correct, these data suggest that pomalidomide and dexamethasone (Pd) is used considerably more, with values of 74%, 31% and 18% for the respective years. The use of daratumumab has increased over time, although this is not a comparator as it is only available through the CDF. Some patients had none of the regimens on the list as a 5L treatment.

2.4 Issue 4: Matching-adjusted indirect comparison (MAIC)

The company responded to five issues raised by the ERG in relation to the MAIC undertaken in the company submission. The ERG accepts the process that the company used to assess which variables are included in the propensity score model. Nevertheless, the ERG notes that it is not possible to state that the final propensity score model is the final model in any MAIC, and residual bias may exist.

2.5 Issue 5: Subsequent treatments within ICARIA-MM

Within the company's base case analysis, the assumed use of subsequent treatments was populated from the ICARIA-MM trial limited to the ten most frequently used treatments, with the duration taken from Kantar Health for Western Europe,[4] if available, and from the literature otherwise. A concern was that daratumumab was used at 5L despite not being recommended for use in the UK with disproportionate use between the arms (7% in the IsaPd arm and 38% in the Pd arm). The company explored four methods to adjust OS for this difference: the Rank Preserving Structural Failure Time (RPSFT) model; the two-stage estimation method (TSE); a Markov Cohort Model approach (MCM); and the Inverse Probability of Censoring Weights (IPCW). The ERG did not have sufficient time to assess the work undertaken by the company to the level it would have liked, but the arguments put forward for excluding the RPSFT, the TSE and the MCM methods appear reasonable.

Using the IPCW method, the HR for OS for IsaPd compared with Pd reduced from 0.494 (95% CI; 0.240; 1.015) in the base case analysis (without adjustment) to [redacted] when OS was adjusted for daratumumab use. This was anticipated given the wider use of daratumumab in the Pd arm that the IsaPd arm. When adjustment was made to account for both daratumumab and lenalidomide use, which was used by 14.3% of patients in the IsaPd arm and by 2.4% in the Pd arm, the HR was estimated to be [redacted]. Scenario analyses were then conducted applying these adjustments, and removing the costs of daratumumab, and also lenalidomide for the second analysis.

The IPCW analysis undertaken by the company showed that when adjustment was made for use of daratumumab, the base case deterministic ICER increased from £102,745 per QALY gained to [redacted] per QALY gained. When adjustment was undertaken for daratumumab use and lenalidomide use, the ICER increased to [redacted] per QALY gained. The company, however, state that the IPCW approach '*is not randomisation based and therefore is likely to be biased by unmeasured factors that*

are associated with receipt of daratumumab or lenalidomide and survival. Results from, or based on, the IPCW analyses therefore should be interpreted very cautiously.'

The ERG comments that the increase is the ICER is to be expected as daratumumab is a relatively expensive intervention and the removal of its cost would be unfavourable to IsaPd due to the higher use in the Pd arm. An additional observation is that the underlying life years gained and QALYs in the Pd arm remained constant in this analysis as these were the data to which the HR were applied. In reality, it is anticipated that the life years and QALYs gained would be lower in the Pd arm due to the lack of daratumumab or lenalidomide in 5L. This limitation is unlikely to impact on the ICER.

2.6 Issue 6: Extrapolation of time-to-event data

As requested by NICE, the company has tested alternative models to extrapolate survival functions than those used within its base case. The company acknowledged considerable uncertainty in the long-term extrapolations (i.e. structural and parameter uncertainty), but chose to report all results as deterministic ICERs; as noted previously, the ERG prefers probabilistic ICERs as these provides a more accurate estimate of the ICER in a non-linear model. The ERG ran the probabilistic version of the updated model using alternative survival models for extrapolation of time-to-event data however the model reported an error when some of the survival models, such the Weibull are chosen. Given limited time available to explore the model, the ERG did not identify the source of the error in the model, and reports only the deterministic results of the analyses performed by the company.

Using a PAS discount of [redacted] the estimate of the ICER in the company's sensitivity analyses ranged from £77,973 to £145,859 per QALY gained, based on alternative OS models. The Bayesian Information Criterion (BIC) indicated that the exponential distribution used in the base case provided the best-fit to the overall survival (OS) data, but with a BIC value less than four lower than the Weibull distribution, (which produced the £145,859 ICER), there was only positive, and not strong evidence to suggest the exponential distribution fitted the data better.[5] The company states that the Weibull distribution may not have clinical plausibility in that all patients would be predicted to have died within 5 years (for Pd) and within 10 years (for IsaPd), whereas with the use of the exponential distribution 10% would be alive on IsaPd at 10 years, with all patients on Pd dead within 10 years. The ERG comments that as the (OS) trial data for IsaPd are immature (maximum follow-up of 28 months), predictions from the models of the proportion of patients alive at 10 years will be uncertain.

The impact of using alternative survival models for extrapolation of progression-free survival had less impact, resulting in ICERs which range from £101,377 to £104,811. There was a larger effect when alternative models were used for time to treatment discontinuation, with all increasing the ICER, with a range from £105,684 to £196,079. The BIC indicated that the exponential distribution used in the

base case was the best-fit to the data, but with a BIC value less than five lower than the log-logistic distribution, there was only positive, and not strong evidence to suggest the exponential distribution fitted the data better.[5]

The company also provided ICERs for IsaPd compared to PanVd. Using the PAS discount of [redacted] all ICERs were in excess of £120,000.

2.7 Issue 7: The time horizon

As suggested by the ERG and the NICE Technical Team, the company has extended the time horizon to 20 years. The ERG is content with this amendment.

2.8 Issue 8: Cost uncertainties within the analysis

The company has amended the model to cost all medication at the start of the cycle, as recommended by the ERG. The ERG is content with the change and its implementation, but notes that no change has been made to the drug administration costs. However, the ERG believes this is a minor issue, and its impact on results is negligible. The company also provided a sensitivity analysis assuming the costs of the full RDI of Pd, which had a moderate impact on the deterministic ICER, increasing it from £102,745 to £110,891. The company additionally provided an analysis whereby drug wastage was not considered; this reduced the base case deterministic ICER to £83,159. The ERG considers neither assumption plausible, but believes this provides useful information to the appraisal committee.

2.9 Issue 9: Health utility values

The company has amended the method of sampling probabilistic utilities in the model so that the average utility value for progression free survival is always greater than the average value for progressed disease. The ERG is content with this change.

2.10 Issue 10: Cancer Drugs Fund

The company '*strongly support the use of the CDF to resolve key uncertainties in the evidence base for this appraisal*' citing that the OS data are immature, that real world evidence is being collected and that further data would allow the impact of re-treatment with an anti-CD38 intervention to be assessed. The company states that '*the critically important assessment of overall survival will require the full duration of the CDF to compare outcomes of ICARIA-MM trial with real-world patients and to provide more confidence about which long-term extrapolation of overall survival is appropriate.*'

[redacted]

[redacted]

2.11 Issue 11: End of life

The company's base case model predicts that patients receiving Pd have a mean undiscounted survival duration of [redacted] years, although estimates from other survival distributions, such as the lognormal and log-logistic models, lead to higher estimates of [redacted] and [redacted] years, respectively. Supportive evidence for the lower estimate is provided by the company which states that '*All the clinical experts we spoke with all agree that life expectancy for patients at 4L is less than 2 years,*' and the company provided estimates from three real-world evidence sources to show that the median OS for those on Pd was lower than 14 months, although the mean values could not be calculated from this information. As discussed in Section 2.5, it is also likely that the average survival in the Pd arm would decrease if the effects of daratumumab and lenalidomide were removed.

The company also reports that the modelled median OS for IsaPd was 33 months and that this is considerably longer than the observed median OS of 14 months for Pd '*suggesting that isatuximab in this treatment setting provides substantial survival benefit.*' The ERG notes that these estimates are not directly comparable, but agrees that the data indicate a survival advantage for IsaPd over Pd.

The ERG comments that the company did not discuss the life expectancy of patients who receive PanVd, presumably because it did not think that it was an appropriate comparison. For the information of the committee, in the company base case comparison of IsaPd and PanVd the modelled mean OS for patients receiving PanVd was [redacted] years, with a survival gain for IsaPd of over [redacted] years.

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