Single Technology Appraisal

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [Review of TA658] [ID4067]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [Review of TA658] [ID4067]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Sanofi:**
   a. Full submission
   b. Summary of Information for Patients (SIP)
   c. Additional Evidence Submission

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Myeloma UK

4. **Expert personal perspectives** from:
   a. Clinical expert, nominated by UK Myeloma Society
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5. **External Assessment Report** prepared by ScHARR

6. **External Assessment Report – factual accuracy check**

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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Document B

Company evidence submission

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Abbreviations

Abbreviation	Definition
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike information criteria
BIC	Bayesian information criterion
BNF	British National Formulary
BOR	Best overall response
BSH	British Society for Haematology
CDF	Cancer Drugs Fund
CEM	Cost-effectiveness model
CI	Confidence interval
CR	Complete response
CRAB	Calcium, renal, anaemia and bone
CSR	Clinical study report
Dara	Daratumumab
DCA	Data collection arrangement
DSU	Decision Support Unit
DVd	Daratumumab in combination with bortezomib, and dexamethasone
DVTd	Daratumumab in combination with bortezomib, thalidomide, and dexamethasone
EAG	External assessment group
EAMS	Early Access to Medicines Scheme
ECOG	Eastern Cooperative Oncology Group
EEPRU	Policy Research Unit in Economic Evaluation of Health and Care Interventions
EHA	European Hematology Association
EMA	European Medicines Agency
eMIT	Electronic market information tool
EoL	End-of-life
EORTC	European Organisation for Research and Treatment
EOT	End of treatment
ERG	Evidence review group
ESMO	European Society for Medical Oncology
ESS	Effective sample size
EU	European Union
GEE	Generalised estimating equations
GLM	Generalised linear model
HES	Hospital episode statistics
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment

Abbreviation	Definition
ICER	Incremental cost-effectiveness ratio
IMiD	Immunomodulatory derivative
IMWG	International Myeloma Working Group
IPCW	Inverse probability of censoring weighting
IPD	Individual patient data
IR	Infusion reaction
IRC	Independent Response Committee
IRT	Interactive response technology
Isa	Isatuximab
IsaPd	Isatuximab + pomalidomide + dexamethasone
ISS	International Staging System
ITT	Intention-to-treat
IV	Intravenous
IxaRd	Ixazomib + lenalidomide + dexamethasone
Kd	Carfilzomib + dexamethasone
KM	Kaplan-Meier
KOL	Key opinion leader
LSM	Least square mean
MAA	Managed access agreement
MAIC	Matching adjusted indirect comparison
MM	Multiple myeloma
MRD	Minimal residual disease
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PanVd	Panobinostat + bortezomib + dexamethasone
PAS	Patient Access Scheme
PASLU	Patient Access Schemes Liaison Unit
Pd	Pomalidomide + dexamethasone
PD	Progressive disease
PFS	Progression-free survival
PH	Proportional hazards
PI	Proteasome inhibitor
PICOS	Population, intervention, comparison, outcomes and study design
PPS	Post-progression survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal social service
QALY	Quality-adjusted life year

Abbreviation	Definition
QoL	Quality of life
R	Lenalidomide
RCS	Restricted cubic spline
RCT	Randomised controlled trial
RDI	Relative dose intensity
RPSFT	Rank-preserving structural failure time
RRMM	Relapsed and refractory multiple myeloma
RWE	Real-world evidence
SACT	Systemic anti-cancer therapy
SAE	Serious adverse event
SC	Subcutaneous
sCR	Stringent complete response
SCT	Stem cell transplant
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard-of-care
TA	Technology appraisal
TEAE	Treatment emergent adverse event
TFI	Treatment-free interval
TLR	Targeted literature review
TSD	Technical support document
TSE	Two-stage estimation
TTD	Time to treatment discontinuation
UK	United Kingdom
UKMF	UK Myeloma Forum
VAS	Visual analogue scale
VGPR	Very good partial response
WTP	Willingness to pay

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

B.1.1. Decision problem

The objective of this technology appraisal is to re-evaluate, following availability via the Cancer Drugs Fund (CDF), the clinical and cost-effectiveness of isatuximab in combination with pomalidomide and dexamethasone (IsaPd) for the treatment of adults with relapsed and refractory multiple myeloma (RRMM) who have received three prior therapies including lenalidomide and a proteasome inhibitor (PI), and whose disease has progressed on their last therapy (corresponds to 4th line treatment of multiple myeloma [MM] in the United Kingdom [UK]). The proposed positioning in this submission is consistent with the original submission and CDF recommendation for IsaPd in this 4th line population (technology appraisal [TA] 658, published 18 November 2020) (1).

IsaPd has been available for use via the CDF since October 2020. Uptake has been significant and sustained with IsaPd clearly addressing an unmet need and is considered a standard of care (SoC) treatment option at 4th line by clinicians (2, 3).

As highlighted in the original appraisal, it was challenging to demonstrate the cost-effectiveness of IsaPd given the now well described issue of showing cost-effectiveness for combinations where the backbone contains a therapy (in this case, pomalidomide) with a price that has already been set at or near the cost-effectiveness threshold (in this case £50,000/quality-adjusted life year [QALY] as end-of-life [EoL] criteria were met). To date, there is still no solution to this challenge, so it remains a significant issue for this reappraisal.

The appraisal of IsaPd has been made more difficult by recent changes to the National Institute for Health and Care Excellence (NICE) methods. The replacement of EoL with severity modifiers has meant that the severe nature of RRMM at 4th line is not adequately accounted for in the severity QALY modifiers, and the effective willingness to pay (WTP) threshold may now be lower than in the original appraisal. A new comparator (daratumumab monotherapy; also assessed at EoL threshold) has also been included as it recently entered routine commissioning. Despite these challenges, Sanofi are committed to seeking routine commissioning for IsaPd. Whilst the eligible population for IsaPd is expected to decline, access to IsaPd is important for eligible patients at 4th line, where median overall survival remains less

than 2 years and progression-free survival (PFS) is less than 6 months with current NICE recommended routinely commissioned treatments.

Given no substantive solution to support access to branded combination therapies exists and the unexpected changes in NICE's methods and processes for CDF reviews, we urge NICE and the appraisal committee to take a pragmatic approach and exert flexibility in their decision making to ensure that patients can continue to have access to IsaPd and that they are not inadvertently disadvantaged by these complex issues.

The decision problem addressed by this submission is outlined 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 or more prior therapies, including lenalidomide and a PI, and have demonstrated disease progression on the last therapy	Adult patients with RRMM who have received three prior therapies, including lenalidomide and a PI, and whose disease progressed on the last therapy (corresponds to 4th line treatment of RRMM).	The population addressed in this submission aligns with the NICE recommendation from TA658 and the population included in the CDF. Mature clinical evidence from the ICARIA-MM trial and UK real world evidence are provided to demonstrate this 4th line population has a high unmet need necessitating the need for continued access to IsaPd in this setting
Intervention	Isatuximab in combination with pomalidomide and dexamethasone	Isatuximab in combination with pomalidomide and dexamethasone	As per scope
Comparator(s)	For people who had two previous therapies: • Ixazomib plus lenalidomide and dexamethasone (subject to NICE evaluation) For people who had three previous therapies: • Daratumumab [TA783] • Ixazomib plus lenalidomide and dexamethasone (subject to NICE evaluation) For people who had three or more previous therapies: • Pomalidomide plus dexamethasone [TA427] • Elranatamab (subject to NICE evaluation) • Ciltacabtagene autoleucel (subject to NICE evaluation) For people who had four previous therapies: • Belantamab mafodotin (subject to NICE evaluation	For people who had three previous therapies: Pomalidomide + dexamethasone Daratumumab monotherapy	The clinical and cost effectiveness evidence submitted is focused on comparators relevant for people who have had three prior therapies only (4th line). As a triplet based IV therapy, IsaPd is likely to be used in patients who are fit enough to receive it and those who are eligible for an anti-CD38 therapy. Pomalidomide + dexamethasone and daratumumab monotherapy are available at 4th line. Clinical opinion suggests that in the real-world following the availability of IsaPd in CDF, these therapies are used in a different patient population - patients not fit enough to tolerate triplet therapy. The rationale for not considering other listed comparators are provided below: IxaRd is not an appropriate comparator as the combination includes lenalidomide and would be prescribed to patients that are not refractory to lenalidomide (the pivotal trial for IxaRd excluded patients that were refractory to lenalidomide) (4). IsaPd is indicated in patients that had received at least two lines of therapy including lenalidomide and PI and have progressed on their last therapy. Therefore, the population eligible for treatment with IxaRd in clinical practice is fundamentally different to those considered for treatment with IsaPd. The patients enrolled in the registrational clinical trials for belantamab mafodotin, and elranatamab are triple-class refractory (refractory to an IMiD, PI and an anti-CD38 antibody). Since IsaPd is an anti-CD38 antibody and IMiD combination, the patients eligible for treatment with IsaPd,

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			(those not previously refractory to an anti-CD38 antibody) would not be prescribed belantamab mafodotin or elranatamab. Furthermore, given that the introduction of anti-CD38 antibody therapies at earlier lines in clinical practice is relatively recent, the majority of anti-CD38 use is at 4th line (either through the availability of IsaPd in the CDF or daratumumab monotherapy [TA783]) (5). Hence belantamab mafodotin and elranatamab are most likely to be used 5th line or later, subject to positive recommendation by NICE expected in June 2023 and Feb 2024, respectively. The ciltacabtagene autoleucel appraisal has been suspended as of 13 March 2023 (6), and the EMA licenced indication is for patients who are triple-refractory (including refractory to anti-CD38 antibody such as isatuximab) (7), therefore will not be considered in this appraisal as a comparator.
Outcomes	PFS OS Response rates Duration of response Time to progression Time to next treatment Time to treatment discontinuation Adverse effects of treatment HRQoL	PFS OS Response rates Duration of response Time to progression Time to next treatment Time to treatment discontinuation Adverse effects of treatment HRQoL	As per final NICE scope.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective.	As per the NICE reference case, the cost-effectiveness of IsaPd is expressed in terms of incremental costs per QALY. Costs have been considered from the NHS and PSS perspective. Additionally, several non-reference case analyses to demonstrate the value of IsaPd are presented. This includes: • Removing backbone cost of non-cost-effective treatments • Analyses considering patent expiry for pomalidomide	Due to recent changes to the NICE methods and processes and ongoing challenges in demonstrating cost effectiveness of combination therapies such as IsaPd, where it is likely that IsaPd would not be cost-effective even if isatuximab was priced at £0, there is a need for flexibility in the appraisal of IsaPd. Therefore, several non-reference case analyses are presented in the economic analyses for consideration.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account	• Applying methodology to demonstrate value attribution to constituent therapies in a combination	
Subgroups to be considered	No subgroups pre-specified in scope	The clinical section of the submission presents evidence from final data cut from ICARIA-MM trial for the 4th line-only post-hoc subgroup.	The clinical section presents updated/final data from the ICARIA-MM trial 4th line-only post-hoc subgroup, relevant to the decision problem addressed in the company submission.
Special considerations including issues related to equity or equality	Not applicable. No special considerations specified in scope	It is not considered that this appraisal will exclude any people protected by equality legislation; or lead to a recommendation that would have a different impact on people protected by equality legislations than on the wider population; or lead to recommendations that would have an adverse impact on people with a particular disability	There are equity considerations worth highlighting in this appraisal. • As a branded combination treatment, IsaPd is not likely to be cost-effective at £0 price for isatuximab, when using the NICE reference case. This remains a challenge as there is no currently solution to address this issue (8-10). • If changes to NICE methods are applied to this appraisal, the EoL criteria will no longer apply. IsaPd may not qualify for a severity weighting given the opportunity cost neutral way in which the severity modifiers were introduced. This disadvantages patients who are towards the end of their life. • Under the new NICE methods, IsaPd is being compared to treatments which were evaluated by NICE under significantly different WTP thresholds. Under the current NICE methods, these comparator treatments may no longer be considered cost-effective.

Source: NICE ID4067 Final Scope 2023 (11). Abbreviations: CDF, Cancer Drugs Fund; DCA, data collection arrangement; EMA, European Medicines Agency; EoL, end-of-life; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; IMiD, immunomodulatory derivative; IsaPd, isatuximab + pomalidomide + dexamethasone; ITT, intention-to-treat; IxaRd, ixazomib + lenalidomide + dexamethasone; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; Pd, pomalidomide + dexamethasone; PFS, progression-free survival; PI, proteasome inhibitor; PSS, personal social services; QALY, quality-adjusted life year; RRMM, relapsed or refractory multiple myeloma; SACT, systemic anti-cancer therapy; UK, United Kingdom.

B.1.2. Description of the technology being evaluated

The summary of product characteristics (SmPC) or prescribing information for use, and the European public assessment report and scientific discussion are provided in Appendix C.

A description of IsaPd is provided in Table 2.

Table 2. Technology being evaluated

UK approved name and brand name	UK approved name: Isatuximab Brand name: SARCLISA®
Mechanism of action	Isatuximab is an IgG1-derived humanised monoclonal antibody, which binds to a specific extracellular epitope of cell surface glycoprotein CD38 that is highly expressed on myeloma cells. In vitro, isatuximab acts through IgG Fc-dependent mechanisms including ADCC, ADCP and CDC. Furthermore, isatuximab can also trigger tumour cell death by induction of apoptosis via an Fc-independent mechanism, as well as inhibition of the enzymatic activity of CD38.
Marketing authorisation/CE mark status	Isatuximab received EMA marketing authorisation valid throughout the EU on 30th May 2020 (12). IsaPd was not separately assessed within MHRA as the converting of CAPs to UK MAs, 'grandfathering' and managing lifecycle changes occurred on 1st January 2021.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Isatuximab is indicated in combination with pomalidomide and dexamethasone, for the treatment of adult patients with RRMM who have received at least two prior therapies including lenalidomide and a PI and have demonstrated disease progression on the last therapy. This is the indication relevant for the current appraisal. Isatuximab is also indicated in combination with carfilzomib and dexamethasone, for the treatment of adult patients with MM who have received at least one prior therapy. This indication is not considered in this submission. 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 10 mg/kg IV infusion, weekly for 4 weeks (cycle 1: days 1, 8, 15, and 22), then every 2 weeks for cycle 2 and beyond (days 1, 15). Each treatment cycle consists of a 28-day period and is repeated until disease progression or unacceptable toxicity. 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 IV, on days 1, 8, 15 and 22 of each 28-day cycle. Dexamethasone should be administered only once prior to isatuximab IV infusion, as part of the backbone treatment and premedication (alongside the other recommended medicinal products) to reduce the risk and severity of 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 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
List price and average cost of a course of treatment	Isatuximab list price (13) • £506.94 (100 mg vial) • £2,534.69 (500 mg vial) The average total cost of IsaPd per patient based on list prices is £206,832.52. The drug costs are calculated for a 73 kg adult; costs are based on median time to discontinuation [redacted] and the relative dose intensity for isatuximab [redacted], pomalidomide [redacted] and dexamethasone [redacted] from ICARIA-MM.
Patient access scheme (if applicable)	A confidential PAS discount of [redacted], agreed with NHS England and PASLU is applied to the list price of isatuximab. Isatuximab PAS price [redacted] The average total cost of IsaPd per patient based on the PAS price of isatuximab is [redacted]. The drug costs are calculated for a 73 kg adult; costs are based on median time to discontinuation ([redacted]) and the relative dose for isatuximab [redacted], pomalidomide [redacted] and dexamethasone [redacted] from ICARIA-MM. In addition to the simple discount patient access scheme, isatuximab is eligible for VPAS payments. This represents an additional 26.5% rebate on net sales of the product in 2023. [redacted]

†Screen tests include antibody detection tests, antibody identification panels, and antihuman globulin crossmatches.
Abbreviations: ADCC, antibody dependent cell mediated cytotoxicity; ADCP, antibody dependent cellular phagocytosis; CAP, centrally authorised products; CDC, complement dependent cytotoxicity; EMA, European Medicines Agency; EU, European Union; IAT, indirect antiglobulin test; IFE, immunofixation; IgG, immunoglobulin; IR, infusion reaction; IsaPd, isatuximab + pomalidomide + dexamethasone; IV, intravenous; MA, marketing authorisation; MHRA, Medicines and Healthcare products Regulatory Agency; MM, multiple myeloma; NHS, National Health Service; PAS, Patient Access Scheme; PASLU, Patient Access Schemes Liaison Unit; PI, proteasome inhibitor; RBC, red blood cell; RRMM, relapsed and refractory multiple myeloma; SmPC, summary of product characteristics; SPE, serum protein electrophoresis; UK, United Kingdom; VPAS, voluntary scheme for branded medicines pricing and access.

B.1.3. Health condition and position of the technology

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 abnormal monoclonal immunoglobulins (14), and by periods of disease remission and relapse, with decreasing treatment response after each relapse (15-18).

MM is an orphan disease with an incidence of approximately 9.7/100,000 population in England and although 80% of patients are aged 60 years or greater, the majority are under 75 years old (19).

Patients with MM report a high symptom burden and there is drastic impact on patients' quality of life (QoL), as well as that of their families or carers (20-24).

The burden of MM was highlighted during the previous appraisal for IsaPd [TA658] (1), with statements provided by Myeloma UK from patients living with MM such as *"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 treatment).

Almost half of patients diagnosed with MM will receive three or more different regimens during their life with the disease (25). However, once a patient becomes refractory to those agents, survival is limited and newer treatment options are needed (16-18).

Isatuximab, in combination with pomalidomide and dexamethasone (IsaPd), is currently recommended for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received three prior lines of treatment (including lenalidomide and a proteasome inhibitor [PI]) via the Cancer Drugs Fund (CDF) (26).

In the 4th line population, there is a continued high unmet medical need despite other available treatments, due to poor median survival at 4th line of less than 2 years (15.6 months to 20.5 months) (27-29).

IsaPd offers a significant improvement in progression-free survival (PFS) (a median PFS of 12.39 months vs 6.54 months with Pd alone) while preserving QoL for patients with MM at 4th line (30).

Real-world data independently collected and published on patients receiving IsaPd in UK clinical practice (n=107), has demonstrated a mean PFS of 10.1 months in a clinical setting; comparable with outcomes observed in the ICARIA-MM trial (31).

Since IsaPd was made available in the CDF, the treatment pathway has evolved where routinely available treatments (daratumumab monotherapy and Pd) are now reserved for patients with poorer performance or those unable to tolerate triplet combination therapy. Four experienced UK haematologists indicated that there is no other treatment available at 4th line that is as effective as IsaPd **(3)**.

B.1.3.1. Disease overview

MM is a malignant, haematopoietic tumour that remains incurable for the vast majority of patients, and is characterised by a clonal proliferation of bone marrow plasma cells that produce abnormal monoclonal immunoglobulins (14). These cells cause skeletal damage such as bone lesions, osteoporosis, and fractures which are all hallmarks of MM (32). The proliferation of malignant plasma cells in the bone marrow limits haematopoiesis, leading to anaemia and recurrent infections (14, 33, 34). Outside of the bone marrow, the overproduction of monoclonal immunoglobulin (known as m- or paraprotein) leads to renal impairment. These characteristics of MM are often referred to as the CRAB features (calcium, renal, anaemia and bone) (35).

The disease is characterised by cycles of remission and relapse, with decreasing treatment response after each relapse (15-18). 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 (14). Progression-free survival (PFS) is therefore, a key endpoint for determining the efficacy of new treatments for patients with RRMM, and continues to be a primary outcome measure in many trials (36).

Sequencing studies have confirmed that MM is a sub-clonal disease; most tumour plasma cells share a common pool of mutations but may differ by several sub-clonal mutations (37). Furthermore, the major subclone at the time of diagnosis may be different from the major sub-clone observed at first relapse, which can also differ from those seen at later relapses (37). Corre et al 2018 reported that chemoresistance and relapse could be induced by newly acquired mutations in myeloma drivers but also by sub-clonal mutations pre-existing to the treatment (37). Almost half of patients diagnosed with MM will receive three or more different regimens during their lifespan (25). However, with each successive line of treatment, decreases in duration of response, survival outcomes and declining quality of life (QoL) are observed and once a patient becomes refractory to those agents, survival is severely limited (27, 28).

With growing resistance to existing treatments, combinations of novel agents with multiple modes of action, such as isatuximab combined with a third-generation immunomodulatory derivative (IMiD) such as pomalidomide, and dexamethasone, offer the potential for synergistic effects with the absence of cross-resistance, leading to improved patient and clinical outcomes.

B.1.3.2. Epidemiology

Although MM is the second most common haematologic malignancy worldwide, it is a rare disease (38, 39). The age-standardised incidence in England between 2016 and 2018 was 9.7/100,000 (19), considerably higher than the global age-standardised incidence rate of 2.1/100,000 (40).

Between 2016 and 2018, there were 5,951 new cases of MM in England each year, accounting for 2% of all new cancer cases (19). Furthermore, there were 3,098 deaths from MM between 2017 and 2019, and the 5-year survival rate is 52.3% (19). Over the last decade, MM incidence rates have increased by approximately 11% in the UK, and are projected to rise a further 11% between 2014 and 2035; this increase is largely a reflection of the changing prevalence of risk

factors and improvements in diagnosis (19). The incidence of MM is highest in the elderly, peaking between the ages of 85–89 years, with 43% of cases diagnosed in patients aged ≥75 years (19).

More men than women are affected by MM (19) and it is also more common in black than in white people (41). Based on data from a cross-sectional chart review conducted in 2014 from seven European Union (EU) countries, including the UK, 15% of patients are expected to reach 4th line (18). Current estimates suggest that ~[redacted] of patients at 4th line are eligible for treatment with anti-CD38 antibody regimens (42), but this is expected to decrease due to the high uptake of anti-CD38 treatments at earlier lines (based on discussions with clinical experts in an advisory board) (3). Furthermore, the population size may be reduced by usage of isatuximab-based combinations specifically earlier in the myeloma treatment pathway (pending positive licensing and reimbursement).

B.1.3.3. Burden of disease

B.1.3.3.1. Clinical burden

MM is often preceded by monoclonal gammopathy (a premalignant condition/stage) (35) and is characterised by cycles of remission and relapse, with decreasing treatment response after each relapse (15-18). Time to progression has been reported to decrease from 18 months with 1st line treatment, to 5 months with 4th line treatment (18), in line with PFS being reported to decrease from 11 months with 1st line treatment, to 7 months with 4th line treatment (16). Overall survival (OS) also decreases as patients progress to subsequent lines of therapy and is particularly poor in patients who have received two or more lines of therapy, with a median OS of 15.6–20.5 months (27-29).

These figures are supported by real-world evidence (RWE) identified in a targeted literature review (TLR) conducted by Sanofi, which reported global estimates of 10.9–18.8 months for OS in patients who had received at least three prior treatment lines (43-54). Median PFS estimates after three prior lines were also estimated to be between 3.4 and 10.9 months in clinical practice (31, 44-54). The short life expectancy at 4th line 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 health technology assessment (HTA) submissions in RRMM at this line (5, 55).

There are four main clinical characteristics of MM; hypercalcaemia, renal impairment, anaemia, and bone lesions, collectively known as CRAB features (35). Hypercalcaemia is present in nearly 20% of patients and is a major but treatable cause of renal insufficiency. However, renal impairment which presents in 20–50% of patients at diagnosis, is caused mainly by the toxic effects of the monoclonal light chains produced by myeloma cells (56). Patients with MM also experience recurrent infections, most likely due to impaired immune response resulting from neutropenia and/or insufficient levels of normal antibodies (57). Bone lesions manifest as lytic lesions, osteoporosis or fractures (57), and may affect as many as 90% of patients over the course of the disease (32).

B.1.3.3.2. Humanistic burden

MM has a drastic impact on patients' QoL, 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 (20-24).

Patients face a wide range of MM-related symptoms, which has a negative impact on their QoL (20, 22, 24). Fatigue, bone pain and tiredness are the most common symptoms, with patients reporting difficulty in taking long walks or carrying out strenuous activities even during low-severity phases of MM (20, 22, 24). In a European multicentre cohort study, in patients with MM or RRMM across four different severity subgroups (i.e. asymptomatic, mildly symptomatic, moderately symptomatic, or severely symptomatic), each severity level was associated with a reduction of ≥6 points in the average score of the distribution of health-related quality of life (HRQoL) (i.e. 'Global Health Status' domain within the European Organisation for Research and Treatment (EORTC) instrument, 'QoL, 'Physical, Functioning', 'Social Functioning' and 'Future Perspective') from the previous symptom level, demonstrating the negative impact of advancement of the disease on the QoL, physical, and social functioning of the patients (22).

Furthermore, in a UK study of 605 patients with MM (58), being in a first treatment-free interval (TFI) (i.e. remission) relative to other treatment phases and experiencing a longer TFI were associated with better HRQoL as assessed by EQ-5D visual analogue scale (VAS) (1st line treatment [standard deviation, SD]: 53 [25], first TFI [SD]: 70 [20]).

Additionally, there is a significant psychological burden of MM. In a qualitative study of 50 patients with RRMM and 30 haematologists, for most patients, the first relapse was associated with the most intense period of negative emotions, including feelings of

hopelessness and resignation, and that the realisation that they had progressed to a relapse caused a larger decline in emotional well-being than that caused by their initial diagnosis (21).

During the previous appraisal for IsaPd [TA658] (1), Myeloma UK provided statements from patients living with MM, adding to published data (21) and highlighting the significant psychological burden brought on by not knowing if there is another line of treatment:

"*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 treatment

"*That uncertainty and thinking you might have come to the end of the road that is so worrying*." Patient on 5th line treatment.

The psychological burden of MM is further highlighted by a cross-sectional survey in which 27.4% of patients with MM reported signs of anxiety and 25.2% reported signs of depression, while 48.8% of the patient's partners also reported signs of anxiety and 13.6% reported signs of depression (59).

The burden also extends to patients family and friends, with Boland et al (2013) (20) reporting that 50% of patients felt their physical function interfered with their family life. Hulin et al (2017) (21) also highlighted that patients perceived their illness as a burden to family and friends, and reported an increased reliance on immediate family for both emotional and physical support. This was further increased with relapses, with many patients feeling guilty about the added emotional and physical burden on their loved ones. Hulin et al (2017) (21) also reported that this burden on family and carers was perceived as a barrier to clinical support, with long waiting times to see specialists, and the burden of repeated hospital visits requiring time investments and potentially an economic impact, not only for the patients, but for family and carers as well.

B.1.3.3.3. Economic burden

The substantial economic impact of RRMM is demonstrated in a study of 307 patients with RRMM (60); only 11% were working (48% of those who were not working indicated it was due to their disease), and 39% of those working reported disease-driven absenteeism of at least

1 day over the last 4 weeks. Of the 80% that were retired, 32% indicated it was an early retirement caused by RRMM. Furthermore, a retrospective cohort study in English hospitals using hospital episode statistics (HES) demonstrated the increase in economic burden as MM progresses, reporting that newly-diagnosed patients on average had 3.32 inpatient admissions and 5.91 outpatient events per year, while this increased to an average of 19.97 inpatient and 14.21 outpatient events per year with movement to further therapy (61).

B.1.3.4. Clinical pathway of care

B.1.3.4.1. Current treatment guidelines

The published treatment guidelines for RRMM include:

- NICE guideline. Myeloma: diagnosis and management (NG35). February 2016. This guideline covers the diagnosis and management of MM in people aged 16 and over (62)
- 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 (63)
- British Society for Haematology (BSH) and UK Myeloma Society (UKMS). Guidelines on the diagnosis, investigation, and initial treatment of myeloma. March 2021. This guideline provides clear guidance on the anti-myeloma management of patients with newly diagnosed MM (64)
- European Hematology Association (EHA) and European Society for Medical Oncology (ESMO). Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. February 2021. These updated guidelines cover diagnosis, staging and risk assessment, treatment recommendations and response evaluation of MM (65).

Treatment access in England is primarily driven by NICE recommendations, and therefore European guidelines are not always implemented in clinical practice.

B.1.3.4.2. Current treatment pathway

The treatment pathway for MM in England (Figure 1) is largely determined by NICE recommendations, with a variety of combinations available to patients depending on eligibility

and response to previous treatment. The choice of treatment at each stage of MM involves a complex decision-making process due to the heterogeneity in plasma cell and disease biology, as well as consideration of patient factors and preferences and can result in patients receiving a varied treatment sequence and making them eligible for different treatment combinations with each relapse.

Due to the heterogeneous and incurable nature of MM, patients typically require multiple lines and adaptation to their treatment to regain disease control. This usually involves drug combination strategies with PIs (i.e. bortezomib, carfilzomib or ixazomib), IMiDs (i.e. thalidomide, lenalidomide or pomalidomide), and/or monoclonal antibodies (e.g. daratumumab [Dara], isatuximab [Isa]), together with steroids such as dexamethasone added to these treatment classes to achieve disease control and address symptom burden, with or without stem cell transplant (SCT). Almost all surviving patients with MM eventually relapse and become refractory to existing treatment options.

The therapeutic goals for patients with RRMM focus on controlling the disease as effectively as possible, while prolonging survival and preserving functioning/QoL (66-68). Choice of treatment is individualised, with comorbidities and age frequently taken into account (69). The results of physical examinations and laboratory tests, disease stage, general health status, symptoms, prior treatment, and the patient's lifestyle and views on QoL are also important factors in treatment selection (62), and as such, the treatment pathway for MM is complex to navigate, particularly at later lines. Hence, the availability of varied treatment options is more critical than ever in clinical practice, to provide patients and physicians choice on the most suitable and more personalised therapeutic approach.

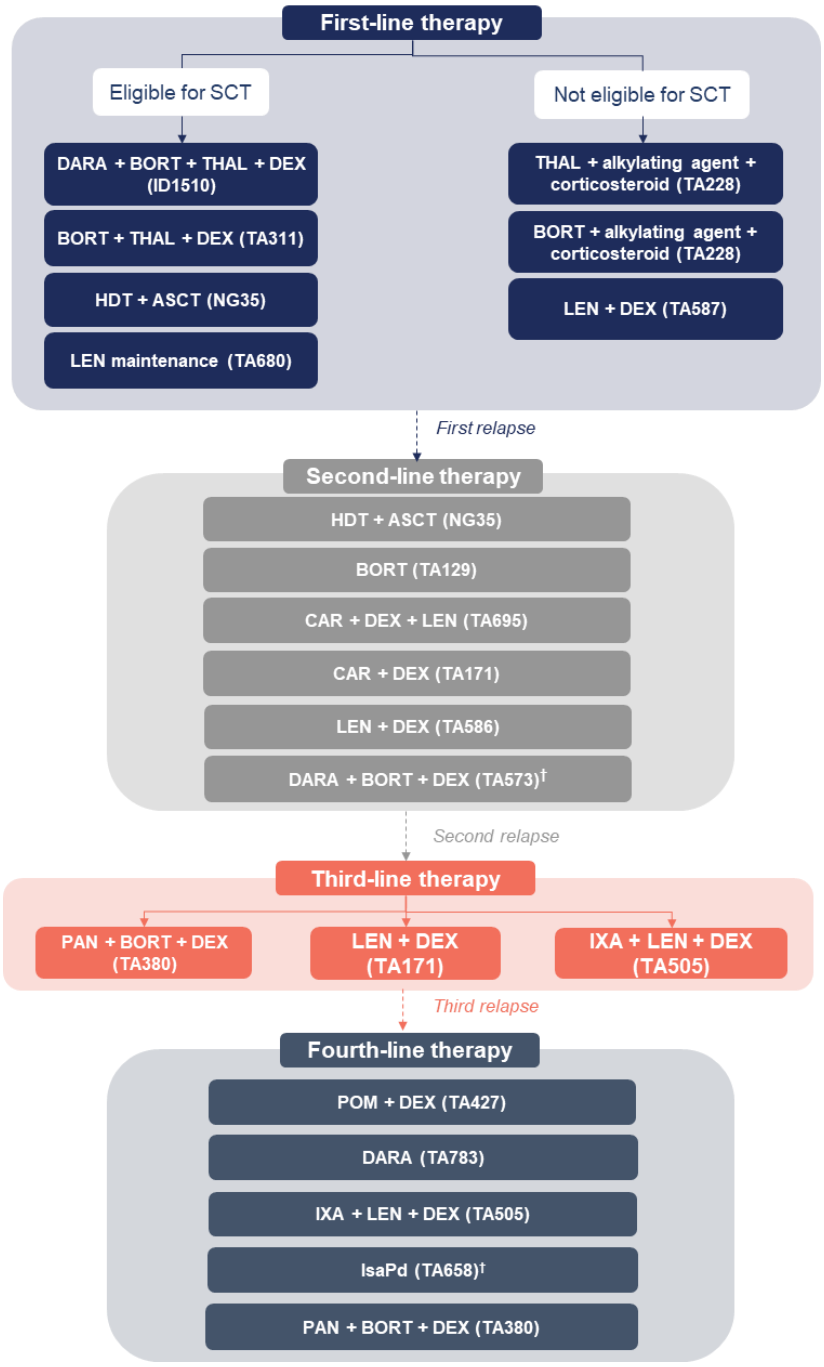
Current treatment options available at 4th line are shown in Figure 1. IsaPd is recommended within the CDF as an option for treating RRMM in adults who have had lenalidomide and a PI, and whose disease has progressed on their last treatment only if they have had three previous lines of treatment (4th line) (26). At 4th line, routinely commissioned treatments include Pd [TA427] (5, 55), daratumumab monotherapy [TA783] (5) and ixazomib with lenalidomide and dexamethasone (IxaRd) (4). The IxaRd combination includes lenalidomide (R) and therefore would only be prescribed to patients that have not relapsed on a lenalidomide-containing regimen in a previous line or are not refractory to it (4). Independently-collected market research data also suggest that IxaRd is predominantly used in 3rd line in clinical practice (42) and

therefore at 4th line, few patients would receive this combination. Reasons for not considering IxaRd as a relevant comparator to IsaPd have been described in Table 1.

Given that daratumumab became available in combination with bortezomib, thalidomide, and dexamethasone (DVTd) at 1st line, a large proportion of transplant eligible patients are now exposed to this combination, but only for fixed-duration cycles as an induction and consolidation regimen; and are therefore unlikely to become refractory to this anti-CD38 antibody. It has also been available as a 2nd line therapy in the CDF (daratumumab + bortezomib + dexamethasone [DVd]) since April 2019 and patients will eventually relapse and/or become refractory to the anti-CD38 therapy. The 4th line population eligible for IsaPd is therefore anticipated to decrease over time, although unlikely to reach zero. According to market share data DVd is used in ~50% of 2nd line patients but not universally; instead, carfilzomib and dexamethasone (Kd) or lenalidomide plus dexamethasone (Rd) may be offered (42). Clinicians in an advisory board agreed that there will remain a continued unmet need as some patients will not have received daratumumab in the earlier stages of treatment or will receive daratumumab but will not become anti-CD38 refractory (3). Furthermore, as the combination of an anti-CD38 and an IMiD is known to give improved outcomes, clinicians expect a need for IsaPd to remain at 4th line.

The treatment landscape in MM is evolving rapidly with new combinations being licensed in the UK – however, reimbursement remains challenging. Several novel therapies with new modes of action have been licensed for use in later lines of therapy for relapsed and refractory patients, however, manufacturer HTA submissions for these products have been terminated, suspended or severely delayed (70-72). As such, relapsed and refractory patients remain a difficult to treat population with limited options. However, Phase 3 studies have demonstrated that triplet regimens including backbone therapies with combinations of dexamethasone, lenalidomide, pomalidomide, or bortezomib, are more efficacious than doublet regimens and can overcome drug resistance, and improve outcomes in patients with RRMM, with limited additional toxic effects (73). This highlights the ongoing unmet need and the need for continued access for patients to IsaPd at this point in the pathway.

Figure 1. Clinical pathway of management for MM



Source: adapted from NICE guideline on diagnosis and management of myeloma [NG35] and lead team presentation for daratumumab monotherapy CDF review of TA510.†Note that this represents therapies that are available in the cancer drugs fund.
Abbreviations: ASCT, autologous stem cell transplant; BORT, bortezomib; CAR, carfilzomib; CDF, Cancer Drugs Fund; DARA, daratumumab monotherapy; DEX, dexamethasone; HDT, high-dose therapy; IXA, ixazomib; LEN, lenalidomide; MM, multiple myeloma; NG, NICE Guidance; NICE, National Institute for Health and Care Excellence; PAN, panobinostat; POM, pomalidomide; SCT, stem cell transplant; TA, technology appraisal; THAL, thalidomide.

B.1.3.4.3. IsaPd place in therapy

IsaPd was recommended for use as a treatment at 4th line in the CDF in November 2020 [TA658] (26). Whilst available on the CDF there has been a substantial and sustained uptake of IsaPd (737 patients via the CDF and Early Access to Medicines Scheme [EAMS]) (74).

Contrary to expectations that this population would have diminished at the point of CDF exit due to use of anti-CD38 treatment earlier in the treatment pathway, market share data suggest that IsaPd is currently used in approximately [redacted] of 4th line patients (42). Clinical opinion of four experienced UK haematologists indicated that there is no other treatment available at 4th line that is as effective as IsaPd (3) and thus consider IsaPd the SoC at 4th line. Clinicians at the advisory board also noted that in the immediate future there will be a continued unmet need for an anti-CD38 combination regimen as some patients will not have received daratumumab in the earlier stages of treatment as it would not have been available (or reimbursed) at the time they were diagnosed. They anticipate that although this population is likely to diminish over time, there will always be a residual number of patients eligible for IsaPd at 4th line.

During the advisory board, it was also noted that in a subset of patients, daratumumab monotherapy is used; this group typically comprises patients with poorer prognosis characterised by older age, poorer Eastern Cooperative Oncology Group (ECOG) performance status (PS) and very low blood counts (e.g. neutrophil and platelet counts). Given the variation in patient characteristics and the incurable nature of MM, it is important to retain all currently available treatment options but also access to more efficacious therapies with fewer and/or manageable toxicities compared with existing therapies (3).

Despite recent advances in treatment and improvements to the treatment pathway, there are limited, optimal treatment options for patients who are refractory to lenalidomide by the 4th line setting due to increased usage in frontline and the extensive use of IxaRd at 3rd line. These heavily pre-treated patients have difficult-to-treat disease, a poorer prognosis and a short life expectancy (75, 76). ICARIA-MM, the pivotal trial supporting the licence of IsaPd enrolled patients that were relapsed and refractory to previous therapy including lenalidomide, and demonstrated PFS benefit for IsaPd compared to Pd (30). The short life expectancy at 4th line has been accepted by previous NICE committees when appraising the Pd and daratumumab submissions, demonstrated by their assessment under the NICE EoL criteria which was applied to all appraisals preceding the introduction of the new NICE methods in January 2022 (5, 55, 77, 78). Treatment-related toxicities further contribute to the burden of RRMM patients (79).

Therefore, there remains a need for alternative options for patients that are still fit to receive combination triplet regimens, particularly as there is possible cross-resistance between treatments from the same therapeutic group, such as the PIs: bortezomib and carfilzomib, or the IMIDs: lenalidomide and pomalidomide (80).

IsaPd offers a significant improvement in PFS while preserving QoL for patients with RRMM at 4th line, evidenced by more recent follow-up from the randomised, Phase 3 pivotal trial ICARIA-MM (Section B.2.6). Real-world data independently collected and published on patients receiving IsaPd in UK clinical practice (n=107), has demonstrated a mean PFS of 10.1 months in a clinical setting; comparable with outcomes observed in the ICARIA-MM trial in the 4th line population (31). The response rate with IsaPd in the ITT population was higher and the duration of response was longer than observed for alternatives (e.g. Pd), and patients typically remain on IsaPd longer than on Pd which is consistent with published data (29, 81). In addition, clinicians are now experienced in the management of AEs relating to IsaPd, e.g. thrombocytopenia and anaemia, and there are no significant concerns with infusion reactions (IRs).

The combination of an anti-CD38 and an IMiD is known to give improved outcomes based on data from other trials such as POLLUX (NCT02076009) and MAIA (NCT02252172) (82, 83). Clinicians opt to use the treatment which offers the longest period of PFS in order to minimise myeloma-associated morbidity (e.g. bone disease, renal issues). In this regard, they noted PFS estimates of less than 6 months for daratumumab in SACT dataset. Therefore, IsaPd would be a valuable and efficacious treatment option for those RRMM patients that remain anti-CD38 naïve and fit to tolerate triplet therapy when they reach 4th line (3).

B.1.4. Equality considerations

Replacement of the EoL modifier (which applied in the original appraisal) with the new severity modifiers may disadvantage patients approaching EoL (84, 85). Compared to the EoL modifier, the lower weightings are reflective of the opportunity cost neutral way in which the severity modifiers were introduced. The absolute shortfall criteria tend not to recognise severity in conditions affecting older populations such as RRMM as life expectancy of the general population would be relatively short. Assuming an average age of 70, it would not be possible to meet the threshold for the maximum severity weighting based on absolute QALY shortfall. However, the cut-off level for proportional shortfall, which does recognise severity regardless of age, is so high that it is extremely difficult to meet. The condition would have to be so severe

that it was associated with a life expectancy of less than 6 months to qualify for the x 1.7 modifier.

Given the appraisals for Pd and daratumumab were concluded before the new NICE manual was published, so were not subjected to the new methods, it is inequitable that IsaPd is assessed under a different framework, particularly as the comparator technologies which were approved on the basis of meeting the EoL criteria, may no longer be considered cost-effective.

B.2. Clinical effectiveness

IsaPd vs Pd

The key clinical trial evidence for the efficacy of isatuximab plus pomalidomide and dexamethasone (IsaPd) compared with the comparator (pomalidomide and dexamethasone [Pd]) comes from the ICARIA-MM phase 3, randomised control trial.

Participants were heavily pre-treated (median of three prior lines), and all were relapsed/refractory to their last regimen which included lenalidomide and a proteasome inhibitor (PI), alone or in combination. Overall, the study population of ICARIA-MM was representative of the UK population with relapsed/refractory multiple myeloma (RRMM) at 4th line.

- In the final data cut (March 2022) in 4**th** line patients, median progression-free survival (PFS) was prolonged in the IsaPd arm (12.39 months [95% confidence interval [CI]; 7.425, 27.663]) compared with the Pd arm (6.54 months [95% CI; 4.468, 10.086])[a]. The stratified hazard ratio (HR) was 0.536 (95% CI: 0.343, 0.840) representing a 46.4% risk reduction of disease progression or death in favour of IsaPd vs Pd (p=0.0057)
- With a median follow-up of 52.4 months (~4 years), the median overall survival (OS) in 4**th** line patients was 33.28 months (95% CI: 18.431, 54.275) in the IsaPd arm vs 17.71 months (95% CI: 11.565, 27.532) in the Pd arm, representing a clinically meaningful improvement in survival vs Pd. The final OS HR was 0.657 (95% CI: 0.409, 1.055)
- QoL as measured by EQ-5D-5L and the EORTC QLQ-C30 score was sustained over time and was similar in both treatment groups demonstrating that there was no decrement in QoL with the addition of an anti-CD38 to a doublet backbone.
- With 3 years of additional follow-up, the overall safety profile of IsaPd remains consistent with previous results (11 October 2018).

During the period of managed access between 2nd December 2019 and 31st March 2022, observational data were collected for IsaPd via the systemic anti-cancer therapy (SACT) dataset (2).

- In the Early Access to Medicines (EAMS) and Cancer Drugs Fund (CDF) cohort (combined cohort (N=737)), the median treatment duration with IsaPd was 8.9 months [95% CI: 7.3, 10.8] with median follow-up of 5.9 months. This is comparable to treatment duration outcomes seen in 4th line population of ICARIA-MM (with longer median follow-up).
- The median OS in the combined cohort was 18.8 months (95% CI: 15.7, 22.9) with a median follow-up for of 9.4 months. Comparisons with trial data are challenging given that SACT data are immature and subject to uncertainty, for example, given the differences in post-study treatment.

Overall, ICARIA-MM provides longer term, head-to-head RCT evidence vs Pd and is the primary data source used to inform the cost-effectiveness comparison vs Pd, in line with the data collection agreement.

IsaPd vs daratumumab monotherapy

In absence of RCT evidence, it was not possible to conduct an anchored ITC or to conduct appropriate adjusted comparisons vs daratumumab monotherapy. Therefore, the best available evidence was considered to be a naïve comparison of SACT data sets.

A naïve comparison between IsaPd SACT and daratumumab monotherapy SACT datasets demonstrated increased median treatment duration for IsaPd (considered a proxy for PFS) (8.9 months [95% CI: 7.3, 10.8]) compared with daratumumab monotherapy (4.5 months [95% CI: 4.3, 4.9]).

[a] After the primary endpoint, further data was not collected centrally by IRC for PFS but reported here is further data from cut-off 14MAR2022 assessed by investigator using the same method as IRC.

B.2.1. Identification and selection of relevant studies

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.

As the de novo SLR was designed to be broad enough to serve a global context, a range of interventions were included, some of which were outside of the NICE scope. For the updated SLR, the interventions in Population, Intervention, Comparison, Outcomes and Study design (PICOS) were restricted to align with the anticipated NICE final scope for this appraisal and included a subset of the interventions (IsaPd, panobinostat in combination with bortezomib and dexamethasone [PanVd], Pd, and daratumumab monotherapy [note that PanVd was not included in the final scope]). Study designs included randomised controlled trials (RCTs) (Phase 2 and above), single-arm clinical trials, and open label extensions or long-term follow-up trials. A summary of the inclusion and exclusion criteria are shown in Table 3 (and Appendix D). The study selection and data collection process were identical for the de novo SLR and SLR update.

Table 3. Eligibility criteria (PICOS) – de novo and update clinical SLR

Characteristics	Inclusion criteria	Exclusion criteria
Population	Adults (aged 18 years and above) diagnosed with RRMM (including Kahler disease, myelomatosis, plasma cell myeloma and medullary plasmacytoma) who have failed at least 2 lines of treatment Studies of mixed populations (for example, studies including patients with 1 or more lines of prior treatment) will only be eligible if outcomes are 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 is eligible	Children (under 18 years) Patients not described as having RRMM Patients who have had fewer than 2 lines of treatment (e.g. newly diagnosed)
Subgroups considered	• Age: <65 vs 65–75 vs >75 years • Number of previous lines of therapy: (2 or 3) vs >3 • Type of prior therapy • High risk patients defined by cytogenetic abnormalities including: ○ del(17p), t(4;14), t(14;16)	–

Characteristics	Inclusion criteria	Exclusion criteria
	○ del(17p), t(4;14), t(14;16): At least one vs none ○ del(17p): Yes vs No • Intermediate risk: ○ t(4;14), gain (1q): Yes vs No • Gender: Male vs female • Race: Caucasian vs Asian vs other • Region of the world: Western countries vs eastern Europe vs Asia vs Other • ECOG PS at baseline: 0 or 1 vs 2 • ISS staging at study entry: I vs II vs III • R-ISS staging at study entry: I vs II vs III • Previous autologous stem-cell transplantation: Yes vs No • MM type at diagnosis: IgG vs non IgG • Baseline creatinine clearance (MDRD formula): >60 ml/min vs <60 ml/min • Refractory: ○ PI: Yes vs No ○ Lenalidomide: Yes vs No ○ IMiD: Yes vs No ○ Double refractory to PI + IMiD ○ Triple refractory • Bone marrow % plasma cells • Renal function • Presence of soft tissue cytomas	
Intervention	IsaPd	Interventions/comparators not listed
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: **De novo SLR:** • Bortezomib • Carfilzomib • Daratumumab • Dexamethasone (high dose/ low dose) • Elotuzumab • Ixazomib • Lenalidomide • Melphalan • Panobinostat • Pomalidomide	

Characteristics	Inclusion criteria	Exclusion criteria
	• Thalidomide • Vorinostat • Bendamustine **Update SLR:** • PanVd • Pd • Daratumumab monotherapy **For the purposes of this submission only studies assessing the following interventions were eligible:** • IsaPd • Pd • Daratumumab monotherapy	
Outcomes	• Progression-free survival • Overall survival • All-cause overall survival • Disease-specific overall survival • Response rates • Complete response • Partial response • Overall response rate • Duration of response • Time to progression • Time on treatment • Time to next treatment • Adverse effects of treatment, specifically: o Any Grade 3 or higher AEs o Any SAE • Withdrawals due to AEs • Discontinuations • Mortality • HRQoL, including: o EORTC-QLQ-C30 o MY20 o EQ-5D-5L/EQ-5D-3L • Measures of patient satisfaction	Outcomes not listed
Study design	• Prospective RCTs (Phase II and above) • Single-arm clinical trials (update SLR only) • Open label extensions or long-term follow-up trials (update SLR only)	• Single-arm clinical trials (de novo SLR only) • Open label extensions or long-term follow-up trials (de novo SLR only) • Retrospective or prospective observational

Characteristics	Inclusion criteria	Exclusion criteria
		studies, including cohort studies • Medical record review/chart review studies • Claims database analyses • Patient registry analyses • Case series • Reviews/editorials/commentaries/letters/news • SLRs/(N)MAs† • In vitro/animal studies/pre-clinical studies
Countries	No restriction	–
Languages	English language publications	Non-English language publications

†Relevant SLRs/NMAs were included at title/abstract screening stage so their bibliographic reference lists could be hand-searched for relevant studies.
Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-3L, EuroQol five dimension three level; EQ-5D-5L, EuroQol five dimension five level; HRQoL, health-related quality of life; IgG, immunoglobulin G; IMiD, immune mediated inflammatory disease; IsaPd, isatuximab + pomalidomide + dexamethasone; ISS, International Staging System; MDRD, Modification of Diet in Renal Disease; MM, multiple myeloma; NMA, network meta-analysis; PanVd, panobinostat in combination with bortezomib and dexamethasone; Pd, pomalidomide + dexamethasone; PI, protease inhibitor; PICOS, population, intervention, comparison, outcomes and study design; RCT, randomised controlled trial; RRMM, relapsed and refractory multiple myeloma; SAE, serious adverse event; SLR, systematic literature review.

B.2.1.1. Results

B.2.1.1.1. De novo clinical SLR

The 2018/2019 de novo clinical SLR searches were originally run in October 2018 and updated in June 2019, and the SLR was presented in TA658 (1). A total of 19,630 publications were identified through the electronic database searches and 283 through the searching of other sources. After the removal of 6,896 duplicates, 13,017 publications were reviewed based on their titles and abstracts. A total of 12,291 publications were excluded at the title/abstract review stage as they did not meet the inclusion criteria for the review, leaving 726 potentially relevant publications that were procured for full-text review. By reviewing the full-text publications, a further 533 publications were excluded, resulting in a total of 193 publications meeting the criteria for final inclusion in the SLR. The 193 included publications reported on 32 unique RCTs (serving the global context with all eligible comparators). Of these, three studies (reported in 16 publications) were deemed relevant for this submission (relevant intervention). The flow of

publications through the de novo SLR is depicted in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram in Appendix D.

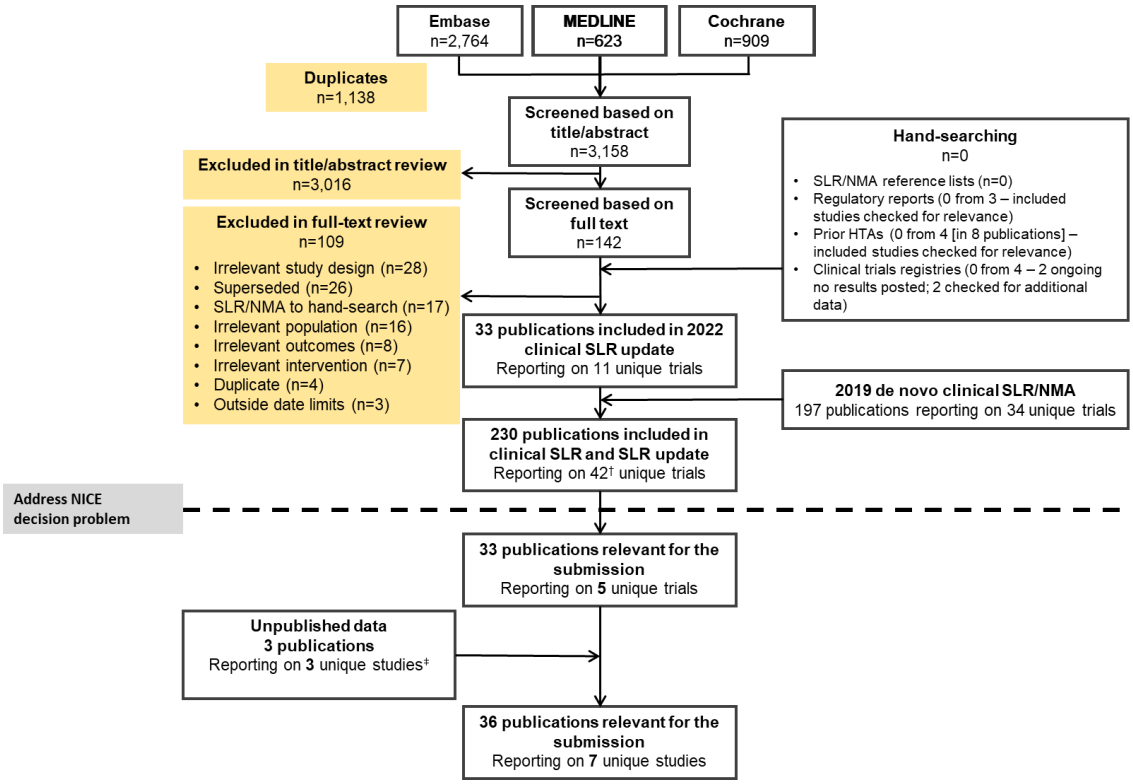
B.2.1.1.2. Update clinical SLR

In the 2022 update clinical SLR, 4,296 publications were identified through the electronic database searches. After the removal of 1,138 duplicates, 3,158 publications were reviewed based on their titles and abstracts. A total of 3,016 publications were excluded at the title/abstract review stage, leaving 142 potentially relevant publications that were procured for full-text review. By reviewing the full-text publications, a further 109 publications were excluded. Hand-searching yielded no additional relevant publications, resulting in a total of 33 publications for final inclusion in the SLR update. These reported on a total of 11 unique trials. Of these, three studies (reported in 15 publications) were deemed relevant for this submission (relevant intervention). These three studies were identified in the original SLR, but additional publications were identified in the updated SLR. The flow of publications through the update clinical SLR is depicted in a PRISMA flow diagram in Appendix D.

B.2.1.1.3. Total included publications (combined de novo SLR and SLR update) relevant to the NICE decision problem

Taken together, 230 publications were included across the de novo SLR and SLR update, reporting on 42 unique trials. The flow of publications through the SLR is depicted in the PRISMA diagram in Figure 2.

Figure 2. PRISMA diagram – total included publications relevant to the NICE decision problem (86)



†Note that the total number of unique trials included in the SLR does not equal the sum of the unique trials identified across the de novo SLR and SLR update, as three of the trials were reported in publications identified in both SLRs.
‡As part of the data collection arrangement within the CDF, SACT data were collected on the use of IsaPd in clinical practice (74). Committee papers from NICE TA783 (5), included the report for the SACT data collected on the use of daratumumab monotherapy in clinical practice (2). In addition, Sanofi provided data for the 4th line subgroup data from the ICARIA-MM CSR (cut-off date 14 March 2022 / 27 January 2022 for OS) (87). The ICARIA-MM trial was identified in the SLR.
Abbreviations: CDF, Cancer Drugs Fund; CSR, clinical study report; IsaPd, isatuximab + pomalidomide + dexamethasone; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial; SACT, systemic anti-cancer therapy; SLR, systematic literature review.

Of the total included studies, five studies (reported in 33 publications) were deemed relevant to the NICE decision problem. One study (ICARIA-MM) referenced in 16 publications (30, 81, 88-101) reported a direct comparison between IsaPd and Pd. Data for the 4th line subgroup data from the ICARIA-MM clinical study report (CSR) (cut-off date 14 March 2022 / 27 January 2022 for OS) was also available (87).

No studies reported direct evidence comparing IsaPd with daratumumab monotherapy; however, four studies (COLUMBA, SIRIUS, REBUILD, and NCT02477891) in 17 publications reported evidence for daratumumab monotherapy that were considered for use in an indirect comparison (50, 102-117) (Table 5).

In addition, as part of the data collection arrangement within the CDF, SACT data were collected on the use of IsaPd in clinical practice (74). Committee papers from NICE TA783 (5), included the report for the SACT data collected on the use of daratumumab monotherapy in clinical practice (2).

Table 4. Identified clinical effectiveness evidence: IsaPd vs Pd

Study name, trial number, phase	Interventions compared	Review	Author, year/source
ICARIA-MM (NCT02990338)	IsaPd vs Pd	De novo SLR (October 2018, updated in June 2019)	Sanofi (protocol) (99); Sanofi (CSR) (30);Richardson 2017a (95); Richardson 2017b (97); Richardson 2018 (96)
		Update SLR (October 2022)	Attal 2019 (81); Beksac 2022 (88); Bringhen 2021 (89); Capra 2020 (90); Dimopoulos 2021 (91); Harrison 2021 (92); Houghton 2019 (93); Hulin 2019 (94); Richardson 2022 (98); Schjesvold 2021 (100); Sunami 2022 (101)
IsaPd SACT	IsaPd	NA	SACT (IsaPd) data report (74)

Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; SACT, systemic anti-cancer therapy; SLR, systematic literature review

Table 5. Identified clinical effectiveness evidence: Daratumumab monotherapy

Study name, trial number, phase	Interventions compared	Review	Author, year/source
SIRIUS	Dara IV	De novo SLR (October 2018, updated in June 2019)	Lonial 2016 (109); CADTH 2016 (102); EMA 2016 (104); FDA 2015 (103); Janssen Research & Development 2013 (106); Lonial 2015 (108); NICE TA510 2017 (118)
		Update SLR (October 2022)	–
COLUMBA	Dara SC vs Dara IV	De novo SLR (October 2018, updated in June 2019)	Mateos 2019 (110); Janssen Research & Development 2017 (107)
		Update SLR (October 2022)	Mateos 2020 (111); Iida 2021 (105); Usmani 2021 (113); Usmani 2022 (114)
NCT02477891	Dara IV	Update SLR (October 2022)	Cook 2021 (115)
REBUILD	Dara IV	–	–
Dara SACT	Dara	NA	SACT (Dara) data report (2)

Abbreviations: CADTH, Canadian Agency for Drugs and Therapeutics in Health; Dara, daratumumab; EMA, European Medicines Agency; FDA, Food and Drug Administration; IV, intravenous; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial; SACT, systemic anticancer therapy; SC, subcutaneous; SLR, systematic literature review.

B.2.2. List of relevant clinical effectiveness evidence

Clinical evidence supporting the marketing authorisation and reimbursement of IsaPd comes from ICARIA-MM, the pivotal Phase 3, RCT investigating the PFS benefit of IsaPd compared with Pd in patients with RRMM. Participants were heavily pre-treated (median of three prior lines) and were all relapsed and refractory to their last regimen and therefore, representative of patients who are at their 4th line of therapy.

As part of the data collection arrangement within the CDF, SACT data were collected on the use of IsaPd in clinical practice (Table 6). Data collection through the SACT dataset could be used to collect evidence on clinical outcomes for people with multiple myeloma who have had three previous lines of treatment and help reduce uncertainty. It also provides information on the proportion of people having treatment after progression on four previous lines of treatment and the treatments used (26).

Table 6. Sources of clinical effectiveness evidence

Study	ICARIA-MM	SACT data cohort study
Study design	Phase III, prospective, randomised open-label, active-controlled multicentre, multinational, double-arm study	NHS England and NHS Digital partnership for collecting and following up real-world SACT data for patients treated through the CDF in England
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	Patients who received IsaPd treatment from 2nd December 2019 to 31st March 2022 in NHS England's Blueteq® database
Intervention(s)	Experimental arm: ITT population (n=154)/Patients at 4th line of treatment (n=52) Isatuximab (SAR650984), 10 mg/kg IV infusion, on days 1, 8, 15, and 22 for 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	IsaPd doses and schedule were not reported. However, treatment was to be provided as per the SmPC for isatuximab and pomalidomide during EAMS and as specified in the MAA.
Comparator(s)	Active comparator arm: ITT population (n=153)/Patients at 4th line 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	Not applicable
Indicate if study supports application for marketing authorisation	Yes	No

Study	ICARIA-MM	SACT data cohort study
Indicate if study used in the economic model	Yes, informs the IsaPd vs Pd comparison	IsaPd vs Pd comparison: • Subsequent therapies from SACT have been included in the base case to account for the cost of post study therapy that are received in UK clinical practice. IsaPd vs daratumumab monotherapy comparison: • A naïve comparison has been performed using SACT data collected for both therapies including treatment duration, overall survival and incorporating subsequent therapies
Rationale if study not used in model	N/A	IsaPd vs Pd comparison: Excluded as primary data source due to availability of robust longer term RCT data from ICARIA-MM and lack of comparable real-world data for Pd from SACT
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	Efficacy outcomes: treatment duration, OS
All other reported outcomes	Refer to B.2.3.1.3	Refer to B.2.3.2.3

Source: Sanofi, Clinical study report, data on file (2022) (30); SACT report (2022) (74).
Abbreviations: CDF, Cancer Drugs Fund; EAMS, Early Access to Medicine Scheme; HRQoL, health-related quality of life; IsaPd, isatuximab + pomalidomide + dexamethasone; ITT, intention-to-treat; IV, intravenous; MAA, managed access agreement; N/A, not applicable; NHS, National Health Service; ORR, overall response rate; OS, overall survival; Pd, pomalidomide + dexamethasone; PFS, progression-free survival; PO, per Os (oral administration); RCT, randomised controlled trial; RRMM, relapsed or refractory multiple myeloma; SACT, Systemic Anti-Cancer Therapy; SmPC, summary of product characteristics; TEAE, treatment-emergent adverse event; TTP, time to progression; UK, United Kingdom.

ICARIA-MM data presented in the previous appraisal of IsaPd [TA658] were from the database lock in October 2018. The key ICARIA-MM data considered in this submission are from the cut-off date 14th March 2022 (PFS) and 27th January 2022 (OS). This represents an additional three years of data on outcomes for IsaPd vs Pd relative to that presented in TA658. The outcomes and database locks used in the previous and current submission are summarised in Table 7.

Table 7. Outcomes available at each datacut for ICARIA-MM vs SACT

	TA658	ID4067 (current appraisal)	IsaPd SACT data cohort study
Median follow-up for PFS	11.6 months	52.4 months	5.9 months
PFS	Y	Y	N/A
Median follow-up for OS	11.6 months	52.4 months	9.4 months
OS	Y	Y	Y
ORR	Y	Y	N/A
QoL	Y	Y	N/A
TTP	Y	Y	N/A
Safety	Y	Y	N/A
Treatment duration	Y	N/A	Y

Source: Sanofi, Clinical study report, data on file (2022) (30); SACT report (2022) (74); NICE TA658 (1, 26)
Abbreviations: N/A, not available; NICE, National Institute for Health and Care Excellence; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; SACT, Systemic Anti-Cancer Therapy; TA, technology appraisal; TTP, time to progression.

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

A summary of the methodology of the ICARIA-MM trial and the SACT data cohort study are provided in Table 8.

Table 8. Summary of study characteristics of ICARIA-MM and SACT

	ICARIA-MM	SACT data cohort study
Trial design	Phase III, prospective, randomised, open-label, active-controlled, multicentre, multinational, double-arm study	Real-world evidence collection via the SACT database
Eligibility criteria for participants	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	Patients who were eligible for Cancer Drugs Fund funding of IsaPd for previously treated MM from 2nd December 2019 to 31st March 2022 in NHS England's Blueteq® database and EAMS Isatuximab plus pomalidomide plus dexamethasone was recommended for use within the Cancer Drugs Fund as an option for treating RRMM in adults who have had lenalidomide and a proteasome inhibitor, and whose disease has progressed on their last treatment, only if they have had 3 previous lines of treatment
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)	24 centres across the UK
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]) Permitted and disallowed concomitant medication	Experimental arm: ITT population (n=154)/Patients at 4th line of treatment (n=52) Isatuximab (SAR650984), 10 mg/kg IV infusion, on days 1, 8, 15, and 22 for Cycle 1, and then on days 1 and 15 for subsequent cycles 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 IV, on days 1, 8, 15 and 22 of each 28- day cycle Active comparator arm: ITT population (n=153)/Patients at 4th line 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	IsaPd (N=737) 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 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 IV, on days 1, 8, 15 and 22 of each 28- day cycle Treatment be provided as per the SmPC for isatuximab and pomalidomide.

	ICARIA-MM	SACT data cohort study
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	Treatment duration OS
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 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	N/A
Pre-planned subgroups	As per previous submission	N/A
Trial number (acronym)	EFC14335 (ICARIA-MM)	N/A

Source: Sanofi, Clinical study report, data on file (2022) (30); SACT report (2022) (74).
Abbreviations: ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; ITT, intention-to-treat; IV, intravenous; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, per OS (oral administration); RRMM, relapsed or refractory multiple myeloma; TEAE, treatment-emergent adverse event; TTP, time to progression; UK, United Kingdom; US, United States.

B.2.3.1. ICARIA-MM

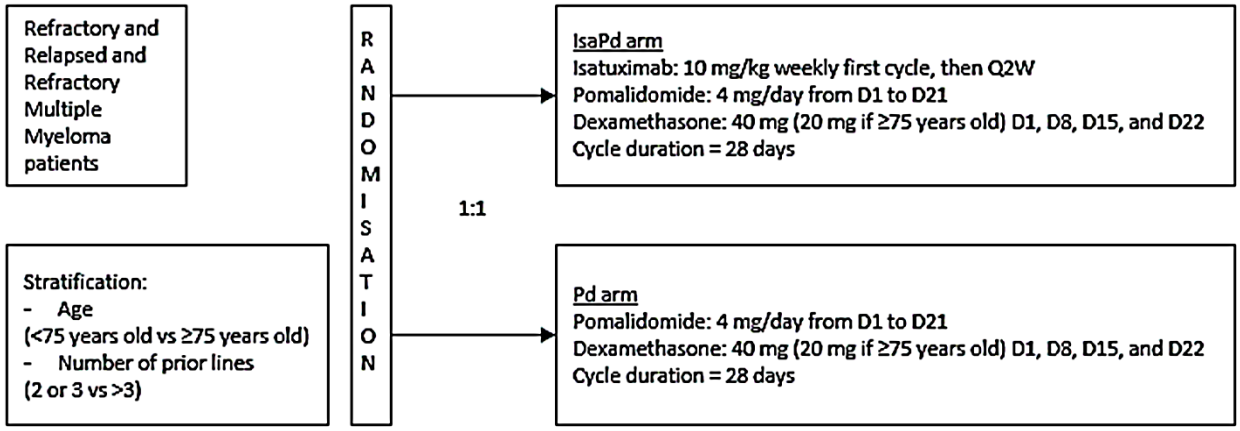
B.2.3.1.1. Study design

ICARIA-MM was a prospective, multicentre, multinational, randomised, open-label, active-controlled, two-arm, Phase III study evaluating the efficacy of IsaPd compared with Pd for the treatment of patients with RRMM who had received at least two prior lines of therapy including lenalidomide and a PI (bortezomib, carfilzomib, or ixazomib) alone or in combination, and had demonstrated progressive disease (PD) on or within 60 days of completion of the last therapy.

Patients were randomly assigned using an interactive response technology (IRT) system in a 1:1 ratio to the IsaPd (experimental) arm or Pd (control) arm. Randomisation was stratified by age (<75 years vs ≥75 years) and number of previous lines of therapy (2 or 3 vs >3). A complete transplant procedure (induction, mobilisation, conditioning, transplant, consolidation, and maintenance) was considered as one line of therapy. Each other subsequent regimen was considered as one line, whatever the reason of discontinuation (progression, AE, or patient request).

The study design is summarised in Figure 3.

Figure 3. Schematic of ICARIA-MM design



Source: Sanofi, Clinical study report, data on file (2022) (30).
Abbreviations: D, day; IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; Q2W, every 2 weeks.

B.2.3.1.2. Eligibility criteria

Key inclusion criteria are listed in Table 9.

Table 9. ICARIA-MM: Key inclusion and exclusion criteria

Key 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 received ≥2 prior lines of anti-myeloma therapy, including ≥2 consecutive cycles of lenalidomide and a proteasome inhibitor alone or in combination
• Patients who failed treatment with lenalidomide and a proteasome inhibitor† 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 earlier response to lenalidomide and/or a proteasome inhibitor, patient had progressed within 6 months after discontinuation of the treatment
• Patients who progressed on or within 60 days after end of the earlier therapy before study entry (i.e. refractory to the previous line of treatment), including the following two categories:
  ○ Refractory disease
  ○ Relapsed and refractory disease

Key exclusion criteria
• Primary refractory MM defined as patients who have never achieved at least a MR with any treatment during the disease course • 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 • Prior therapy with pomalidomide • Any anti-myeloma drug treatment (including dexamethasone) within 14 days before randomisation • Prior allogenic HSC transplant with active GvHD any grade and/or were under immunosuppressive treatment within the last 2 months • 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 • Hypersensitivity to any of the components of study therapy that are not amenable to premedication with steroids • 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 or patient's inability to comply with the study procedures

Source: Sanofi, Clinical study report, data on file (2022) (30).
Notes: †bortezomib, carfilzomib or ixazomib.
Abbreviations: AL, amyloid-light; ALT, alanine aminotransferase; ANC, absolute neutrophils count; AST, aspartate aminotransferase; BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; FLC, Free Light Chain; GvHD, graft vs host disease; HIV, human immunodeficiency virus; HSC, hematopoietic stem cell; MM, multiple myeloma; MR, minimal response; ULN, upper limit of normal.

B.2.3.1.3. Outcomes

Primary endpoints

The primary endpoint was PFS, defined as the time from date of randomisation to the date of first documentation of progressive disease (as determined by an independent response committee [IRC]) or the date of death from any cause, whichever came first. The primary endpoint was centrally assessed and determined by the IRC using central laboratory data for M-protein and central review of imaging.

Key secondary endpoints

Key secondary endpoints were:

Overall response rate (ORR): 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), assessed by the IRC using the International Myeloma Working Group (IMWG) criteria. For patients with non-measurable M-protein on Cycle 1 Day 1, the possible responses were CR, non-PD or PD.

OS: the time from the date of randomisation to date of death from any cause. OS was censored at the last date that the patient was known to be alive or at the cut-off date, whichever was first.

Other secondary efficacy endpoints

Additional secondary endpoints were overall response (i.e. VGPR or better; CR; and sCR), time to response, duration of response, time to progression, immunogenicity, pharmacokinetic profile of isatuximab in combination with pomalidomide, QoL, and safety. Response and disease progression were determined by the independent response committee using the IMWG response criteria.

The exploratory endpoint of minimal residual disease was assessed by the Adaptive clonoSEQ Assay (version 2.0; Adaptive Biotechnologies, Seattle, WA, USA) using bone marrow aspirate samples collected at screening, at the time of confirmation of CR or sCR, and three months later in case of minimal residual disease (MRD) positivity.

B.2.3.1.4. Baseline characteristics

At baseline, the 4th line patients (the focus of this submission) were generally aligned with the overall population and comparable between the two treatment arms. The mean age was

66.1 years and 64.2 years in the IsaPd arm and the Pd arm respectively (Table 11). 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 (>88%) showing a baseline ECOG PS score ≤1. 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%).

B.2.3.2. IsaPd SACT data cohort study

B.2.3.2.1. Study design

Observational data were collected for IsaPd via the SACT dataset (comprising the CDF and EAMS cohorts) between 2nd December 2019 and 31st March 2022 to support treatment duration and subsequent treatments (2). Data in the SACT report provided by NHS Digital reported outcomes for the two cohorts separately and for both cohorts combined. A summary of the SACT data reported for the combined cohort including treatment duration and OS for patients treated with IsaPd are provided in Section B.2.6.2. Data reported for each cohort individually are reported in Appendix O.

The CDF applications included patients from 15 October 2020 to 31 March 2022. A total of 662 patients contributed to the final analysis.

The EAMS ran from 2 December 2019 to 14 October 2020. In total, 75 patients were included.

B.2.3.2.2. Eligibility criteria

Key treatment criteria within the CDF are listed in Table 10 and were broadly consistent across the EAMS and CDF cohorts.

Table 10. SACT inclusion criteria

Key inclusion criteria
Patients aged ≥18 with documented diagnosis of MM
Three prior lines of treatment
≥2 consecutive cycles of lenalidomide alone or in combination and has failed treatment with lenalidomide on account of disease progression, refractory disease or intolerance
≥2 consecutive cycles of a proteasome inhibitor alone or in combination and has failed treatment with a proteasome inhibitor on account of disease progression, refractory disease or intolerance
Responded to ≥1 previous line of treatment i.e. the patient does not have primary refractory myeloma
Refractory to the last line of therapy i.e. there was progression on or within 60 days of the end of the last line of active anti-myeloma systemic therapy
Either no previous therapy with any anti-CD38 antibody (e.g. daratumumab) or if there has been previous treatment with an anti-CD38 antibody, then the patient has received isatuximab via the EAMS scheme or did not progress whilst still receiving an anti-CD38 therapy other than isatuximab or did not progress within 60 days of the last infusion of an anti-CD38 treatment other than isatuximab
No prior treatment with pomalidomide either as monotherapy or within combination therapy
Isatuximab is only to be used in combination with pomalidomide and dexamethasone and not with any other active systemic agents for myeloma
Isatuximab is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment
ECOG performance status of 0, 1 or 2
A formal medical review as to how isatuximab in combination with pomalidomide and dexamethasone is being tolerated and whether treatment with isatuximab in combination with pomalidomide and dexamethasone should continue or not, will be scheduled to occur at least by the end of the second month of treatment
When a treatment break of more than 6 weeks beyond the expected cycle length is needed, a treatment break approval form will be completed to restart treatment, including as appropriate if the patient had an extended break because of COVID 19
Isatuximab and pomalidomide will otherwise be used as set out in their respective SmPCs

Source: SACT report (2022) (74).
Abbreviations: EAMS, Early Access to Medicines Scheme; ECOG, Eastern Cooperative Oncology Group; MM, multiple myeloma; SACT, Systemic Anti-Cancer Therapy; SmPC, Summary of Product Characteristics.

B.2.3.2.3. Outcomes

B.2.3.2.3.1. Treatment duration

Treatment duration was calculated from the start of a patient's treatment to their last known treatment date in SACT. Treatment start date was defined as the date the patient started their CDF treatment. This date was identified as the patient's earliest treatment date recorded in the SACT dataset for the treatment of interest.

B.2.3.2.3.2. Overall survival

OS was calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date was calculated using the patient's earliest

treatment date, and the patient's date of death or the date the patient was traced for their vital status (censored).

B.2.3.2.4. Baseline characteristics

The SACT dataset only reported age, sex, and ECOG performance status, which limits the extent to which the SACT dataset can be compared with the ICARIA-MM trial 4th line population. The median ages were broadly comparable, with a slightly older population in the CDF cohort compared to the IsaPd arm of the ICARIA-MM 4th line population (CDF: median age 71 years, EAMS: 66 years, vs ICARIA-MM IsaPd arm: 68 years). The SACT dataset contained a slightly higher proportion of males than the ICARIA-MM trial (CDF: 61%, EAMS 65%, vs ICARIA-MM IsaPd arm: 57.7%). The SACT dataset also contained a lower proportion of patients with an ECOG 0 performance status than the ICARIA-MM trial (CDF: 19%, EAMS 33%, vs ICARIA-MM IsaPd arm: 40.4%) suggesting a less fit population than the ICARIA-MM trial, as perhaps expected in the real-world.

Baseline characteristics for the SACT cohorts are presented alongside those from the ICARIA-MM trial 4th line population (Table 11). Characteristics for the SACT combined cohort were not reported separately.

Table 11. Baseline characteristics- ICARIA-MM (4th line) and IsaPd SACT data cohorts

	ICARIA-MM 4th line		IsaPd SACT data	
	Pd	IsaPd	CDF cohort (IsaPd)	EAMS cohort (IsaPd)
Baseline characteristic	(n=58)	(n=52)	(n=662)	(n=75)
Age, years, mean (SD)	64.2 (8.9)	66.1 (8.5)	–	–
Age, years, median	65.5	68.0	71	66
Age group, years, n (%)				
<40	–	–	3 (0.5†)	2 (2.7†)
40–49	–	–	23 (3.5†)	2 (2.7†)
50–59	–	–	94 (14.2†)	16 (21.3†)
60–69	–	–	179 (27.0†)	28 (37.3†)
70–79	–	–	273 (41.2†)	24 (32.0†)
≥80	–	–	90 (13.6†)	3 (4.0)
<65	27 (46.6)	19 (36.5)	–	–
65–74	22 (37.9)	26 (50.0)	–	–
≥75	9 (15.5)	7 (13.5)	–	–
Sex, n (%)				
Female	31 (53.4)	22 (42.3)	401 (60.6†)	49 (65.3†)
Male	27 (46.6)	30 (57.7)	261 (39.4†)	26 (34.7†)
Race, n (%)				
White	51 (87.9)	42 (80.8)	–	–
Black or African American	1 (1.7)	0	–	–
Asian	5 (8.6)	5 (9.6)	–	–
Native Hawaiian or other Pacific Islander	0	2 (3.8)	–	–
Missing/Not reported	1 (1.7)	3 (5.8)	–	–
Ethnicity, n (%)				
Hispanic or Latino	1 (1.9)	3 (6.7)	–	–
Not Hispanic or Latino	51 (98.1)	42 (93.3)	–	–
ECOG PS, n (%)				
0	30 (51.7)	21 (40.4)	124 (18.7†)	25 (33.3†)
1	23 (39.7)	25 (48.1)	259 (39.1†)	27 (36.0†)

	ICARIA-MM 4th line		IsaPd SACT data	
	Pd	IsaPd	CDF cohort (IsaPd)	EAMS cohort (IsaPd)
2	5 (8.6)	6 (11.5)	92 (13.9†)	6 (8.0†)
3	–	–	5 (0.8†)	0
4	–	–	1 (<0.2†)	0
Missing	–	–	181 (27.3†)	17 (22.7†)
Geographical region, n (%)				
Western Europe	29 (50.0)	19 (36.5)	–	–
Eastern Europe	10 (17.2)	13 (25.0)	–	–
North America	0	3 (5.8)	–	–
Asia	5 (8.6)	5 (9.6)	–	–
Other countries‡	14 (24.1)	12 (23.1)	–	–
Regulatory region, n (%)				
Western countries	33 (56.9)	27 (51.9)	–	–
Other countries‡	25 (43.1)	25 (48.1)	–	–
Refractory status, n (%)				
Relapsed and refractory¶	58 (100)	52 (100)	–	–
Refractory to lenalidomide	51 (87.9)	48 (92.3)	–	–
Refractory to PI	40 (69.0)	40 (76.9)	–	–

Source: Sanofi, Clinical study report, data on file (2022) (30); SACT report (2022) (74).
Notes: †Percentages calculated by researchers based on available SACT data; Other countries: ‡: Australia, New Zealand, Turkey, and Russia, Czechia, Hungary, Poland, Slovakia, Japan, Korea, Taiwan, Turkey, and Russia; ¶Excluding primary refractory.
Abbreviations: CDF, Cancer Drugs Fund; EAMS, Early Access to Medicines Scheme; ECOG PS, Eastern Cooperative Oncology Group performance status; IsaPd, isatuximab + pomalidomide + dexamethasone; N/n, number of patients; Pd, pomalidomide + dexamethasone; PI, proteasome inhibitor; SACT, Systemic Anti-Cancer Therapy; SD, standard deviation.

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

A summary of statistical analysis methods for the evidence identified in Section B.2.1 is provided in Table 12. Details of the numbers of participants eligible to enter the studies are provided in Appendix D.

Table 12. Summary of statistical analyses

Trial number (acronym)	ICARIA-MM
Hypothesis objective	To demonstrate the benefit of IsaPd in the prolongation of PFS as compared with Pd in patients with RRMM
Analysis sets	Definitions of the populations analysed in ICARIA-MM are listed below: 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.
Sample size, power calculation	The sample size calculation was based on the primary efficacy endpoint (PFS), using the following assumptions: Pd arm had a median PFS of 4.0 months IsaPd arm had 40% risk reduction in HR vs 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 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 vs 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 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, patient withdrawal	Data management ICARIA-MM is a closed study. The pre-specified required number of 220 OS events occurred on 27th January 2022, which was the OS cut-off date for the primary OS analysis. Efficacy and safety analysis are reported as of the 8th April 2022 final data cut Data entry and validation were conducted 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 withdrawal 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)
Statistical analysis	Primary efficacy analysis 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 HR scale was 0.734 Sensitivity analyses 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: PFS analysis without censoring for further anti-myeloma treatment PFS analysis using investigator assessment of response (based on local laboratory M-protein laboratory results and local radiology results) 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 Initiation of further anti-myeloma treatment considered as a PFS event 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

Source: Sanofi, Clinical study report, data on file (2022) (30).
Abbreviations: CI, confidence interval; HR, hazard ratio; IRT, interactive response technology; IsaPd, isatuximab + pomalidomide + dexamethasone; ITT, intention-to-treat; OS, overall survival; Pd, pomalidomide + dexamethasone; PFS, progression-free survival; RRMM, relapsed or refractory multiple myeloma.

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

A complete quality assessment for ICARIA-MM is provided in Appendix D.

The SACT registry contains information from National Health Service (NHS) England providers on all patients treated with anti-cancer therapies. Analysis of the SACT dataset provides information on real-world treatment patterns and treatment outcomes. These data are widely used by NICE to provide information on drugs approved for use within the CDF. Typically, these data act as a secondary source of information alongside primary results from clinical trials.

A key strength of the SACT database is the detailed clinical information collected with whole population coverage for England, which increases the external validity of findings. Data should be entered into the SACT portal every time a therapy is prescribed, as well as the outcomes associated with treatment. Such granularity of data collection enables in-depth exploration of all the drugs prescribed to patients throughout the course of their treatment. The NICE RWE framework (119) notes that studies using real-world data are at risk of bias from a number of sources. Key bias risks include selection bias, information bias and confounding. As a real-world database collecting routine data at the point of care, data quality in the SACT dataset can vary. Some components are notably missing; for example, the proportion of participants with missing ECOG PS data as seen for IsaPd SACT data, or may be incorrectly submitted (2).

B.2.6. Clinical effectiveness results

B.2.6.1. ICARIA-MM trial

This section presents post-hoc analysis of subgroup data for the 4th line population within ICARIA-MM. This is in line the current NICE recommendation for IsaPd in TA658 (1, 26). Data from the intention-to-treat (ITT) analysis of the ICARIA-MM trial are reported in Appendix M.

B.2.6.1.1. Primary endpoint - PFS

At the final analysis, in the 4th line population (N=58 and N=52 in the Pd and IsaPd arms, respectively), median PFS[b] was prolonged in the IsaPd arm (12.39 months [95% CI; 7.425, 27.663]) in comparison with the Pd arm (6.54 months [95% CI; 4.468, 10.086]) (Figure 4). The stratified HR was 0.536 (95% CI: 0.343, 0.840) representing a 46.4% risk reduction of disease progression or death in favour of IsaPd vs Pd (Table 13), continuing to demonstrate a clear PFS benefit for IsaPd vs Pd. This compares with a HR of 0.598 (95% CI: 0.348, 1.030) for IRC determined PFS in the 4th line subgroup at the time of the previous submission.

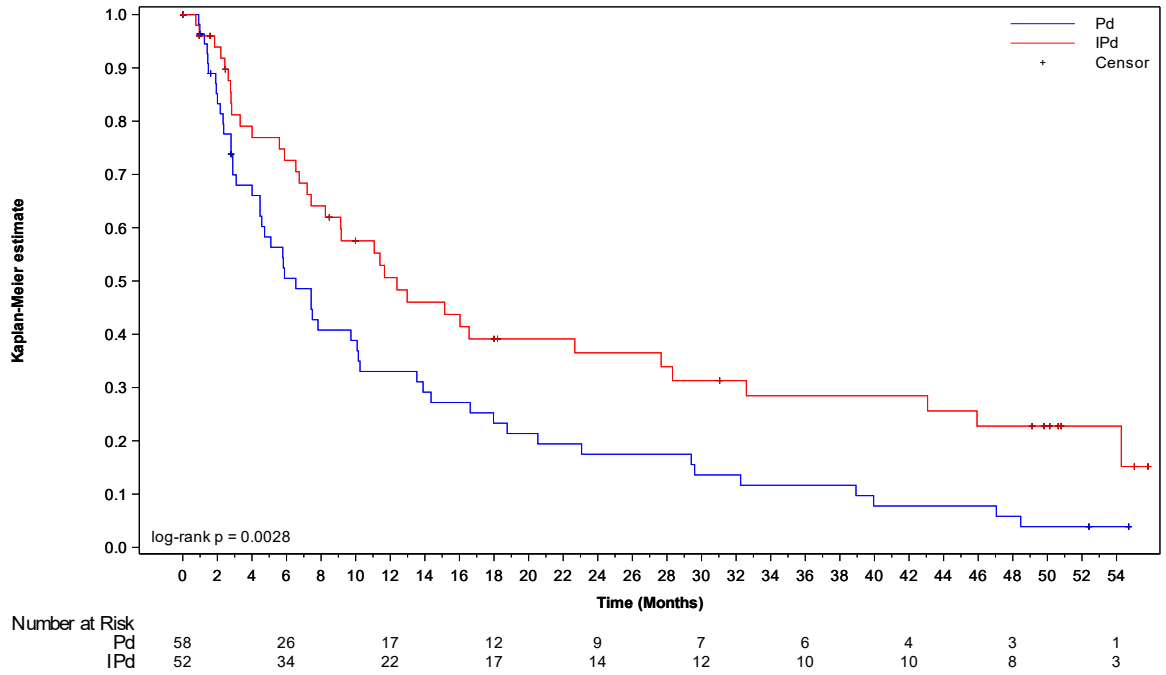
Table 13. ICARIA-MM primary efficacy outcome – PFS† in the 4th line subgroup

	Pd (N=58)	**IsaPd (N=52)**
Number (%) of events	50 (86.2)	35 (67.3)
Number (%) of patients censored	8 (13.8)	17 (32.7)
Kaplan-Meier estimates of PFS in months		
25% quartile (95% CI)	2.79 (1.906, 4.468)	5.59 (2.628, 8.246)
Median (95% CI)	6.54 (4.468, 10.086)	12.39 (7.425, 27.663)
75% quartile (95% CI)	17.97 (10.086, 29.602)	45.93 (22.669, NC)
P value‡¶	0.0057	
HR (95% CI) vs Pd‡	0.536 (0.343, 0.840)	
PFS probability (95% CI)§		
6 months	0.505 (0.363, 0.631)	0.726 (0.576, 0.831)
12 months	0.330 (0.208, 0.458)	0.506 (0.355, 0.639)
18 months	0.233 (0.129, 0.355)	0.391 (0.251, 0.529)
24 months	0.175 (0.086, 0.289)	0.365 (0.227, 0.504)
Number of patients at risk		
6 months	26	34
12 months	17	22
18 months	12	17
24 months	9	14

Source: Sanofi, Clinical study report fourth-line analysis, data on file (2022) (87), cut-off date: 14th March 2022.
†PFS based on disease assessment by the investigator and ignoring symptomatic deterioration; ‡stratified on age (<75 years vs ≥75 years) according to IRT; ¶ one-sided significance level is 0.025; § estimated using the Kaplan-Meier method.
Abbreviations: CI, confidence interval; HR, hazard ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; PFS, progression-free survival.

[b] PFS based on disease assessment by the investigator and ignoring symptomatic deterioration.

Figure 4. PFS – 4th line population analysis based on disease assessment by the investigator and ignoring symptomatic deterioration - Kaplan-Meier curves by treatment group



Source: Sanofi, Clinical study report fourth-line analysis, data on file (2022) (87), cut-off date: 14th March 2022.
Notes: Log-rank p value: Stratified on age (<75 years vs >=75 years) according to IRT. One-sided significance level is 0.025.
Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; PFS, progression-free survival.

B.2.6.1.2. Key secondary endpoints

B.2.6.1.2.1. Overall survival

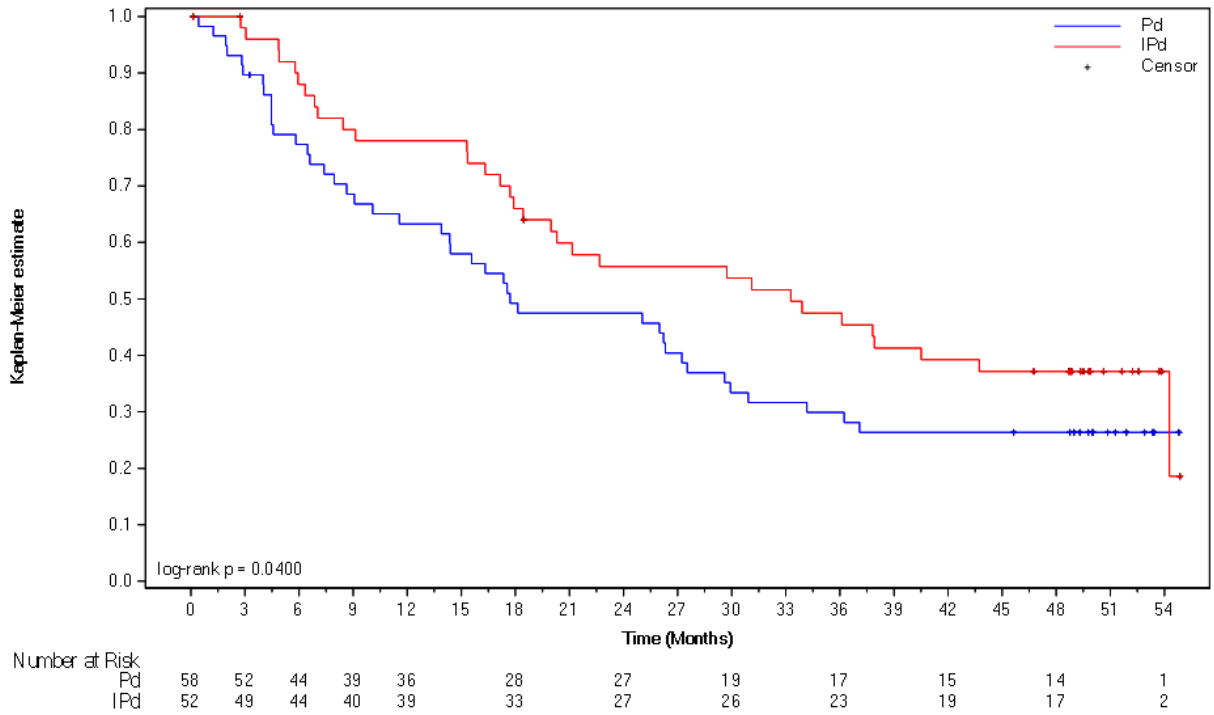
In the 4th line population, the final OS analysis showed that the HR was 0.657 (95% CI: 0.409, 1.055). Median OS was 33.28 months (95% CI: 18.431, 54.275) in the IsaPd arm and 17.71 months (95% CI: 11.565, 27.532) in the Pd arm (Figure 5). At cut-off date for OS (27th January 2022), there were 38.5% of patients in the IsaPd arm and 27.6% of patients in the Pd arm that remained censored, and therefore, there are limited number of patients informing the tail of the Kaplan-Meier (KM).

Table 14. ICARIA-MM secondary efficacy outcome – OS

	4th line subgroup‡	
	Pd (N=58)	**IsaPd (N=52)**
Number (%) of deaths	42 (72.4)	32 (61.5)
Number (%) of patients censored	16 (27.6)	20 (38.5)
Kaplan-Meier estimates of OS in months		
25% quartile (95% CI)	6.60 (4.041, 11.565)	15.34 (6.341, 19.975)
Median (95% CI)	17.71 (11.565, 27.532)	33.28 (18.431, 54.275)
75% quartile (95% CI)	NC (27.532, NC)	54.28 (43.729, NC)
P value¶§	0.080	
HR (95% CI) vs Pd¶	0.657 (0.409, 1.055)	
Survival probability (95% CI)		
12 months	0.633 (0.494, 0.743)	0.780 (0.638, 0.872)
18 months	0.492 (0.358, 0.613)	0.660 (0.511, 0.773)
24 months	0.475 (0.341, 0.597)	0.557 (0.409, 0.682)
Number of patients at risk		
12 months	36	39
18 months	28	33
24 months	27	27

Source: Sanofi, Clinical study report fourth-line analysis, data on file (2022) (87). ‡cut-off date 27th Jan 2022; ¶stratified on age (<75 years vs ≥75 years) according to IRT; § one-sided significance level is 0.025.
Abbreviations: CI, confidence interval; HR, hazard ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; ITT, intention-to-treat; NC, not computable; OS, overall survival; Pd, pomalidomide + dexamethasone; PD, progressed disease.

Figure 5. Overall survival† - Kaplan-Meier curves by treatment group - 4th line subgroup



Source: Sanofi, Clinical study report fourth-line analysis, data on file (2022) (87).
†cut-off date 27th Jan 2022.
Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; ITT, intention-to-treat; OS, overall survival; Pd, pomalidomide + dexamethasone.

Exploratory adjustments for the impact of subsequent therapies on OS - 4th line

At the final analysis, of those who discontinued treatment, more patients in the Pd arm (n=23) received daratumumab as a subsequent therapy compared with the IsaPd arm (n=8). The use of daratumumab in 5th line+ is not permitted in UK clinical practice. Other therapies that were received as subsequent therapies in both treatment arms more frequently and would not be available in UK were lenalidomide and carfilzomib (Table 15). Given the lower use of lenalidomide in the dataset in both treatment arms, it is unlikely to have a significant impact on survival outcomes. The use of carfilzomib as subsequent therapy was similar across the two arms, and likely to have a similar impact on survival in both arms, therefore the overall treatment effect is likely to remain consistent.

Table 15. Subsequent therapies received by ICARIA-MM patients that discontinued study treatment at 4th line†

Treatment	IsaPd		Pd	
	N=52		N=58	
Item	**Patient**	**%**	**Patient**	**%**
Patients who discontinued, N	44		56	
Carfilzomib	17	38.6%	16	28.6%
Cyclophosphamide	14	31.8%	18	32.1%
Daratumumab	8	18.2%	23	41.1%
Bortezomib	10	22.7%	13	23.2%
Melphalan	10	22.7%	4	7.1%
Bendamustine	7	15.9%	5	8.9%
Pomalidomide	6	13.6%	6	10.7%
Lenalidomide	5	11.4%	4	7.1%
Doxorubicin	5	11.4%	2	3.6%
Belantamab	2	4.5%	2	3.6%
Cisplatin	3	6.8%	1	1.8%
Etoposide	3	6.8%	1	1.8%
AutoSCT	2	4.5%	2	3.6%
Ixazomib	1	2.3%	2	3.6%
Panobinostat	1	2.3%	2	3.6%
Selinexor	1	2.3%	2	3.6%
Teclistamab	2	4.5%	1	1.8%
Venetoclax	3	6.8%	0	0.0%
Cobimetinib	2	4.5%	0	0.0%
Isatuximab	1	2.3%	1	1.8%
Thalidomide	2	4.5%	0	0.0%
Atezolizumab	1	2.3%	0	0.0%
CAT-T	0	0.0%	1	1.8%

†Patients can have discontinued but not progressed. This table includes all patients that have discontinued treatment regardless of reason for subsequent therapy receipt. Abbreviations: CAR-T, chimeric antigen receptor T-cell therapy; IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; SCT, stem cell therapy.

Therefore, the main adjustment considered was that for daratumumab where the difference is more prominent and most likely to differentially impact survival across the two arms. The adjustment for daratumumab as subsequent therapy was conducted for the initial company submission [TA658] and hence was updated with more recent data (Table 15). To estimate the treatment effect in absence of receipt of subsequent anti-cancer therapy with daratumumab, exploratory sensitivity analyses using the inverse probability of censoring

weighting (IPCW) method and a simple two-stage estimation (TSE) were performed (further detail provided in Appendix N).

Table 16. ICARIA-MM secondary efficacy outcome – OS† – sensitivity analyses by further therapy with daratumumab, 4th line population

Analysis	IsaPd vs Pd OS HR (95% CI)
4th line unadjusted	0.657 (0.409 - 1.055) †
IPCW adjustment	0.650 (0.373 - 1.132) †
Simple TSE adjustment	0.618 (0.378 - 1.009) †‡

†Stratified by age (<75 years vs >=75 years) according to IRT; ‡ Assuming normal distribution of ln (HR) with standard error based on standard deviation of bootstrap estimates.
Cut-off date: 27JAN2022. Median follow-up time = 52.44 months. HR<1 favours IsaPd arm
Abbreviations: CI, confidence interval, HR, hazard ratio; IPCW, inverse probability of censoring weighting; IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; Pd, pomalidomide + dexamethasone; TSE, two-stage estimation.

There are generally relatively few patients relapsing at 4th line and receiving daratumumab subsequent therapy and so any adjustments will be associated with uncertainty. Furthermore, these adjustment methods typically serve to adjust crossover from comparator to active intervention arm, whereas in these analyses we attempt to adjust for receipt of other subsequent therapies and in both treatment arms. Overall, the analyses suggest that adjusting both treatment arms do not impact the relative treatment effect vs Pd to a large extent. The treatment effect for the adjusted analyses remained generally comparable with the trial HR for the 4th line population, which supports our use of the trial HR for OS in the base case analyses vs Pd and may be considered a conservative estimate of treatment effect. However, caution should be applied in the interpretation of these adjustments given the small sample size and the assumptions made by both methods which are discussed in Appendix N.

B.2.6.1.3. Other exploratory endpoints

A summary of the results for other exploratory efficacy outcomes assessed in the ICARIA-MM trial (data cut: 14 March 2022) are presented in Table 17. Of note, in the 4th line population, 5 patients were minimal residual disease (MRD) negative at 10^{-4} sensitivity level, 4 patients were MRD negative at 10^{-5} sensitivity level, and 1 patient was MRD negative at 10^{-6} sensitivity level in the IsaPd arm. No patients in the Pd arm were MRD negative at any level. MRD negativity has been associated with improved survival outcomes regardless of disease setting (newly diagnosed or relapsed/refractory) and have been accepted as a surrogate for PFS and OS outcomes in earlier lines of treatment in multiple myeloma by NICE [TA763] (120, 121). Additionally, the median KM estimates for time from randomisation to progression on second-line therapy (PFS2) was higher in the IsaPd arm than the Pd arm

(19.12 months [95% CI: 15.014, 37.815] vs 14.39 months [95% CI: 9.068, 19.450], respectively).

Table 17. Summary of the results for other exploratory efficacy outcomes in the ICARIA-MM trial (data cut: 14th March 2022)

Other secondary efficacy outcomes	ICARIA-MM 4th line patients	
	Pd	IsaPd
MRD status		
Number (%) of patients with ≥one sample	1	6
With ≥two samples		
Number (%) of patients MRD negative at sensitivity level		
1 in 10^{4}†	0/1	5/6 (83.3)
1 in 10^{5}†	0/1	4/6 (66.7)
1 in 10^{6}†	0/1	1/6 (16.7)
PFS2		
Number (%) of events	47 (81.0)	35 (67.3)
Number (%) of patients censored	11 (19.0)	17 (32.7)
Kaplan-Meier estimates of PFS2 in months		
25% quantile (95% CI)	6.60 (4.041, 9.068)	9.13 (6.341, 15.310)
Median (95% CI)	14.39 (9.068, 19.450)	19.12 (15.014, 37.815)
75% quantile (95% CI)	30.26 (19.450, NC)	54.28 (26.809, NC)
P value‡	0.0682	
HR (95% CI) vs Pd¶	0.660 (0.420, 1.035)	
PFS2 probability (95% CI)¶		
6 Months	0.773 (0.641, 0.861)	0.880 (0.752, 0.944)
12 Months	0.545 (0.407, 0.663)	0.700 (0.553, 0.807)
18 Months	0.422 (0.293, 0.545)	0.540 (0.393, 0.666)
24 Months	0.334 (0.216, 0.456)	0.395 (0.259, 0.527)

Source: Sanofi, Clinical study report fourth-line analysis, data on file (2022) (87). Cut-off date: 14MAR2022 HR<1 favours IsaPd arm.
†Respective minimum sensitivity of 1 in 10x nucleated cells. ‡Stratified on age (<75 years vs >=75 years) according to IRT; [b]One-sided significance level is 0.025; ¶Estimated using + Kaplan-Meier method.
Abbreviations: CI, confidence interval; IsaPd, isatuximab + pomalidomide and dexamethasone; MRD, minimal residual disease; Pd, pomalidomide + dexamethasone; PD, progressed disease; PFS2, time from randomisation to progression on next line of treatment or death from any cause; SD, standard deviation.

B.2.6.1.3.1. Time to definitive treatment discontinuation – 4th line population

Overall, the time to definitive treatment discontinuation in the 4th line population was significantly delayed in the IsaPd arm compared with the Pd arm. The stratified HR was [redacted] (95% CI: [redacted]). The median time to definitive treatment discontinuation in the IsaPd arm was [redacted] vs [redacted] in the Pd arm, indicating that the addition of isatuximab to Pd treatment resulted in a significant delay of treatment discontinuation ([redacted]).

B.2.6.1.3.2. EQ-5D-5L (datacut: 14 March 2022)

HRQoL for 4th line patients, as measured by EQ-5D-5L health state utility value (HSUV) and EQ-5D-5L VAS, was sustained over time, and similar in both treatment groups (Table 18 and Table 19). At the end of the follow-up period, worsening in health state utilities and health status for 4th line 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 18. ICARIA-MM key secondary endpoint – EQ-5D-5L HSUV, 4th line (safety population*)

Timepoint	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 (0.24)	0.04 (0.24)	0.74 (0.25)	0.00 (0.20)
Treatment Cycle 3‡	0.73 (0.21)	0.03 (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 (0.17)	–0.00 (0.30)	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 (0.22)	–0.00 (0.24)	0.77 (0.14)	0.03 (0.13)
Treatment Cycle 14‡	0.73 (0.23)	0.06 (0.28)	0.80 (0.14)	0.07 (0.14)
Treatment Cycle 15‡¶	0.72 (0.24)	0.11 (0.35)	0.79 (0.18)	0.02 (0.10)
EOT§	0.58 (0.33)	–0.12 (0.32)	0.45 (0.30)	–0.27 (0.19)

* 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; ‡At Day 1.¶ One patient was added at cycle 3 and because more data were collected at cycle 15, this cycle was added to the EQ-5D-5L descriptive analysis; §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 + dexamethasone; MM, multiple myeloma; Pd, pomalidomide + dexamethasone; SD, standard deviation.

Table 19. ICARIA-MM key secondary endpoint – visual analogue scale – EQ-5D-5L, 4th line (safety population*)

Timepoint	Pd (N=53)		IsaPd (N=49)	
	Observed	CFB score†	Observed	CFB score†
Baseline, Mean (SD)	64.17 (19.66)	–	68.46 (19.96)	–
Treatment cycle 2‡	65.20 (19.28)	1.31 (18.76)	66.64 (19.38)	–1.18 (19.64)
Treatment cycle 3‡	68.84 (16.86)	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‡	66.76 (15.96)	1.52 (23.25)	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‡	69.44 (12.17)	1.63 (23.55)	70.45 (13.89)	–2.55 (15.78)
Treatment cycle 14‡	71.73 (15.99)	6.36 (23.59)	75.77 (14.37)	2.92 (15.59)
Treatment cycle 15‡¶	72.33 (15.56)	9.89 (25.75)	74.36 (14.47)	-0.55 (12.36)
EOT§	58.50 (20.19)	–5.81 (20.63)	50.06 (21.03)	-10.94 (20.69)

* 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; ‡ At Day 1; ¶ One patient was added at cycle 3 and because more data were collected at cycle 15, this cycle was added to the EQ-5D-5L descriptive analysis; §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; EOT, end-of-treatment; IsaPd, isatuximab + pomalidomide + dexamethasone; MM, multiple myeloma; Pd, pomalidomide + dexamethasone; SD, standard deviation.

B.2.6.1.3.3. EORTC QLQ C30 (data cut: 14 March 2022)

HRQoL for 4th line patients, as measured by EORTC QLQ C30 Global Health Status, was sustained over time, and similar in both treatment groups (Table 20). At the end of the follow-up period, worsening in health status for 4th line 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 20. ICARIA-MM secondary endpoint - EORTC QLQ C30 – Global health status score, 4th line (safety population*)

Timepoint	Pd (N=53)		IsaPd (N=49)	
	Observed	CFB score	Observed	CFB score
Baseline, Mean (SD)	60.06 (22.25)	–	63.61 (18.99)	–
Treatment cycle 2‡	62.15 (21.26)	0.69 (22.14)	63.52 (19.40)	–0.74 (17.57)
Treatment cycle 3‡	64.92 (17.68)	1.16 (20.70)	62.22 (20.23)	–1.30 (18.97)
Treatment cycle 4‡	63.54 (18.94)	0.63 (26.11)	62.21 (19.87)	–1.74 (14.61)
Treatment cycle 5‡	64.46 (19.60)	2.70 (26.01)	63.16 (18.95)	–0.88 (15.23)
Treatment cycle 6‡	62.96 (20.84)	4.32 (23.27)	64.41 (17.20)	–0.45 (17.78)
Treatment cycle 7‡	59.82 (21.76)	0.00 (25.15)	66.19 (17.84)	1.67 (15.76)
Treatment cycle 8‡	62.15 (18.39)	–1.04 (18.44)	62.37 (22.83)	–1.77 (17.15)
Treatment cycle 9‡	62.32 (18.44)	–1.09 (18.34)	63.10 (19.83)	–1.79 (18.48)
Treatment cycle 10‡	65.48 (16.93)	3.17 (18.72)	70.83 (12.93)	3.87 (13.89)
Treatment cycle 11‡	62.70 (17.20)	3.57 (26.03)	65.38 (15.22)	0.00 (18.56)
Treatment cycle 12‡	65.69 (12.80)	0.00 (16.14)	65.08 (13.60)	–0.40 (17.57)
Treatment cycle 13‡	62.50 (15.81)	–2.08 (15.66)	65.42 (17.58)	1.25 (21.16)
Treatment cycle 14‡	62.12 (23.68)	–3.79 (22.16)	72.44 (13.34)	10.26 (14.50)
Treatment cycle 15‡	69.44 (21.25)	2.78 (25.00)	68.94 (14.95)	8.33 (16.67)
EOT§	47.76 (24.78)	–12.18 (25.63)	35.65 (19.97)	–25.00 (16.17)

*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; ‡ At Day 1. §End-of-treatment: 30 days after last study treatment administration.
Abbreviations: CFB, change from baseline; EOT, end-of-treatment; IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; SD, standard deviation.

B.2.6.2. SACT data cohort study

Results for IsaPd are presented in this section related to the combined cohort. Results for the EAMS cohort and CDF cohort, separately, are presented in Appendix O. Results for the CDF cohort were broadly aligned with those reported for the combined cohort, while results for the EAMS cohort were marginally improved relative to the combined cohort.

B.2.6.2.1. Treatment duration – CDF and EAMS combined cohort

Of the 737 patients with CDF and EAMS applications (combined cohort), 393 (53%) completed treatment by 30 April 2022 (latest follow-up from SACT dataset) (Table 21).[c] The median follow-up time in SACT was 5.9 months (179 days).[d]

Table 21. Breakdown by patients' treatment status

Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	215	29
Patient died – on treatment	97	13
Treatment stopped	81	11
Treatment ongoing	344	47
Total	737	100

Source: SACT report (2022) (74).
Notes: Figures may not sum to 100% due to rounding.
Abbreviations: SACT, Systemic Anti-Cancer Therapy.

The median treatment duration for all patients (combined cohort) was 8.9 months [95% CI: 7.3, 10.8] (270 days) (N=736).[e] Table 22 presents treatment duration at 6-, 12-, 18- and 24-month intervals, and Figure 6 provides the KM curve for treatment duration censored on 30 April 2022.

[c] Patients were assumed to have completed treatment if they had died, had an outcome summary recorded in the SACT dataset, or had not received treatment with IsaPd in ≥3 months

[d] The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

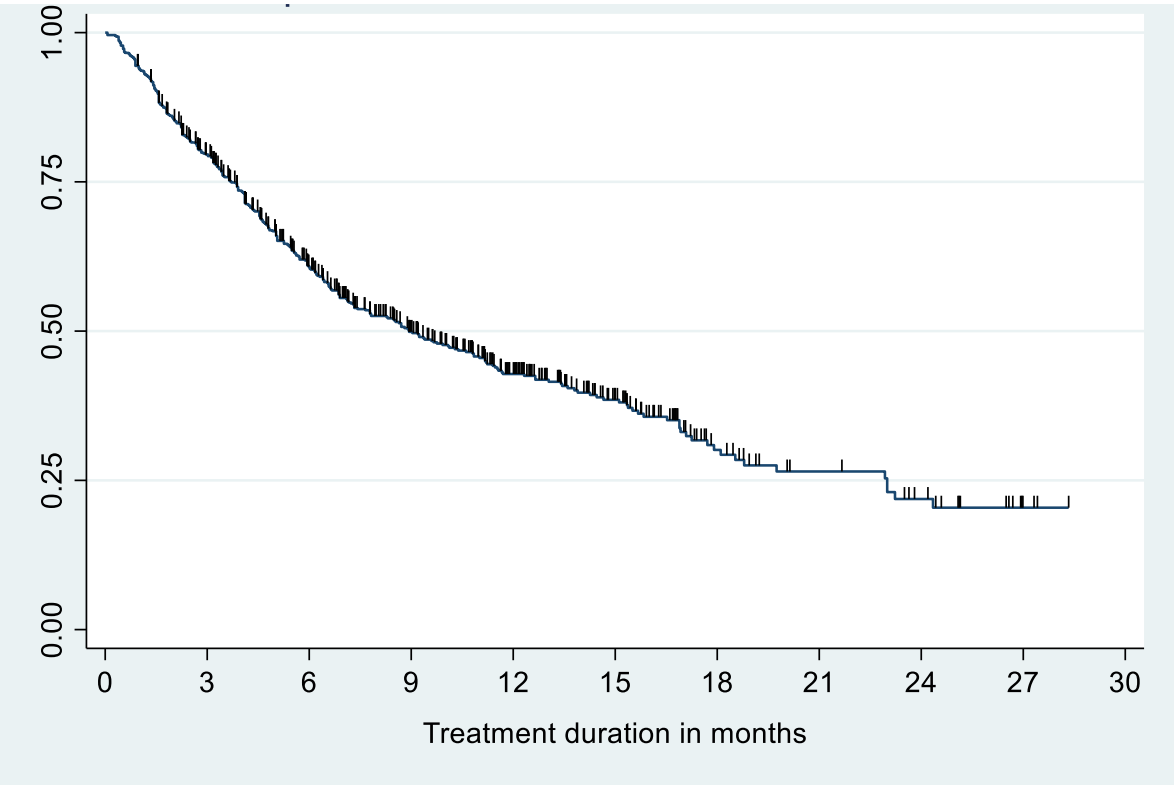
[e] One patient died on the same day they started treatment, and as such, they were excluded from the model as their treatment duration was zero days.

Table 22. Treatment duration at 6-, 12-, 18- and 24-month intervals

Time period	Treatment duration, % (95% CI)
6 months	61 (57, 64)
12 months	43 (39, 47)
18 months	30 (25, 36)
24 months	22 (16, 28)

Source: SACT report (2022) (74).
Abbreviations: CI, confidence interval; SACT, systemic anti-cancer therapy.

Figure 6. Kaplan-Meier Treatment duration (N=736), IsaPd



Source: SACT report (2022) (74).
Notes: One patient died on the same day they started treatment, and as such, they were excluded from the model as their treatment duration was zero days.
Abbreviations: SACT, Systemic Anti-Cancer Therapy.

B.2.6.2.2. Overall survival – CDF and EAMS combined cohort

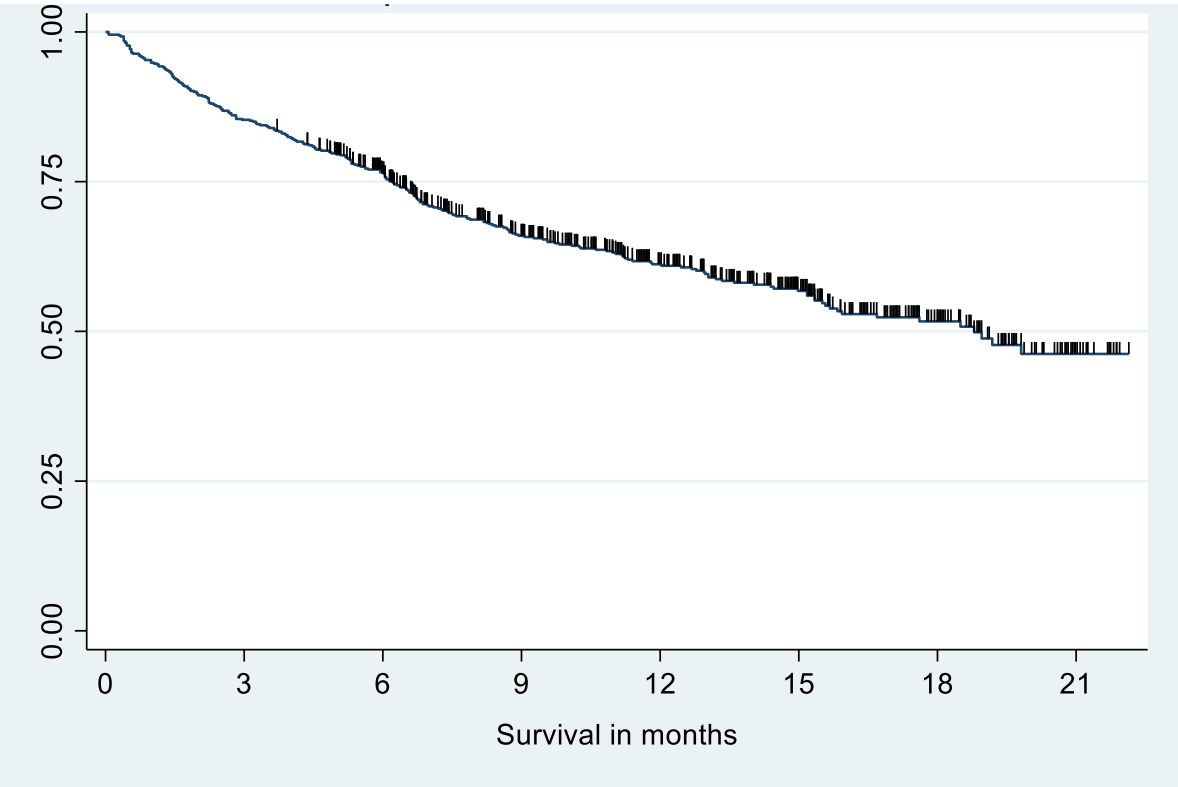
The minimum follow-up was 4.8 months (146 days), and the median follow-up was 9.4 months (286 days). The median OS was 18.8 months (95% CI: 15.7, 22.9) (572 days), and the OS at 6, 12, 18 and 24-month intervals are shown in Table 23. Figure 7 provides the KM curve for OS, censored on 24 August 2022. At last follow-up, more than 50% of patients were censored for an OS event in the IsaPd SACT data.

Table 23. SACT OS at 6-, 12-, 18- and 24-month intervals

Time period	OS, KM% (95% CI)
6 months	77 (73, 80)
12 months	61 (58, 65)
18 months	51 (47, 56)
24 months	42 (36, 48)

Source: SACT report (2022) (74).
Abbreviations: KM, Kaplan-Meier; OS, overall survival; SACT, Systemic Anti-Cancer Therapy.

Figure 7. Kaplan-Meier Overall survival plot (N=736), IsaPd



Source: SACT report (2022) (74).
Notes: One patient died on the same day they started treatment, and as such, they were excluded from the model as their treatment duration was zero days.
Abbreviations: SACT, Systemic Anti-Cancer Therapy.

B.2.6.2.3. Time to and distribution of subsequent treatments

In the CDF cohort, a total of 101/662 (15%) patients treated with IsaPd in the CDF received subsequent therapies, after the patient's last IsaPd cycle. The median time from a patient's last IsaPd cycle in SACT to their next treatment was 19 days. The median time from a patient's first IsaPd cycle in SACT to their next treatment was 133 days.

In total, 22/75 (29%) patients treated with IsaPd via EAMS received subsequent therapies after the patient's last IsaPd cycle. The median time from a patient's last IsaPd cycle in

SACT to their next treatment was 25.5 days. The median time from a patient's first IsaPd cycle in SACT to their next treatment was 179 days.

Table 24 reports regimens first prescribed after IsaPd, as recorded in the SACT dataset; some patients have more than one subsequent therapy, these regimens are shown in Table 25. Subsequent therapies were not explicitly reported for the combined cohort. Advisory board feedback from clinicians suggests that if patients receive IsaPd at 4th line there are currently no effective treatments options in the subsequent lines of therapy. These patients would typically receive PanVd which many patients would not be able to tolerate so a large proportion of patients would be treated palliatively. It is anticipated that as more therapies are approved, long-term survival would improve (3).

Table 24. Distribution of first treatments prescribed after a patient's last IsaPd cycle

Regimen	CDF		EAMS	
	Number of subsequent treatments	%	Number of subsequent treatments	%
Bortezomib + panobinostat	46	46	12	57
Belantamab mafodotin	10	10	3	14
Melphalan	7	7	1	5
Cyclophosphamide	6	6	–	–
Trial unspecified	5	5	2	10
Bortezomib	4	4	–	–
Melphalan + thalidomide	4	4	1	5
Bortezomib + melphalan	3	3	–	–
Bendamustine + thalidomide	2	2	–	–
Cyclophosphamide + thalidomide	2	2	–	–
Pomalidomide	2	2	–	–
Bendamustine	1	1	–	–
Bortezomib + cisplatin + cyclophosphamide + doxorubicin + etoposide + thalidomide	1	1	–	–
Bortezomib + doxorubicin	1	1	–	–
Carfilzomib	1	1	–	–
Carmustine + cytarabine + etoposide + melphalan + rituximab	1	1	–	–
Cisplatin + cytarabine + etoposide	1	1	–	–
Cyclophosphamide + pomalidomide	1	1	–	–
Daratumumab	1	1	–	–

Regimen	CDF		EAMS	
	Number of subsequent treatments	%	Number of subsequent treatments	%
Etoposide + idarubicin + thalidomide	1	1	–	–
Idarubicin	1	1	–	–
Bortezomib + selinexor	–	–	1	5
Cisplatin + cyclophosphamide + doxorubicin + etoposide + thalidomide	–	–	1	5
Thalidomide	–	–	1	5
Total	**101**	**100**	**22**	**100**

Source: SACT report (2022) (74).
Abbreviations: CDF, Cancer Drugs Fund; EAMS Early Access to Medicines Scheme; SACT, Systemic Anti-Cancer Therapy.

Table 25. Distribution of further lines of therapy following a patient's last IsaPd cycle

Regimen	CDF		EAMS	
	Number of subsequent treatments	%	Number of subsequent treatments	%
Belantamab mafodotin	5	5	3	14
Cyclophosphamide	5	5	–	–
Cyclophosphamide + thalidomide	2	2	–	–
Bendamustine	2	2	–	–
Carfilzomib	1	1	–	–
Cyclophosphamide + doxorubicin + vincristine	1	1	–	–
Venetoclax	1	1	–	–
Melphalan + thalidomide	1	1	1	5
Bortezomib + Panobinostat	1	1	12	57
Etoposide + idarubicin + thalidomide	1	1		
Melphalan	1	1	1	5
Trial unspecified	–	–	2	10
Cisplatin + cyclophosphamide + doxorubicin + etoposide + thalidomide	–	–	1	5
Thalidomide	–	–	1	5
Bortezomib + Selinexor	–	–	1	5
Total number of subsequent treatments	**21**	**100**	**22**	**100**

Source: SACT report (2022) (74).
Abbreviations: CDF, Cancer Drugs Fund; EAMS Early Access to Medicines Scheme; SACT, Systemic Anti-Cancer Therapy.

B.2.7. Subgroup analysis

Post-hoc analyses of relevant clinical outcomes for a subgroup of patients in the ICARIA−MM trial at 4th line of treatment are presented in Section B.2.6.1, aligned with the current NICE recommendation [TA658] and decision problem relevant to this appraisal (1, 26). Analysis for the ITT population can be provided on request.

B.2.8. Meta-analysis

Only one relevant RCT evaluating IsaPd was identified and therefore, no meta-analysis was performed.

B.2.9. Indirect and mixed treatment comparisons

B.2.9.1. IsaPd vs Pd

No evidence synthesis is required for IsaPd vs Pd, as relevant efficacy data for the economic model were derived directly from the subgroup of patients in ICARIA-MM who received three prior lines of treatment (4th line population) including lenalidomide and a PI. This post-hoc subgroup was accepted for decision-making at the previous NICE appraisal for IsaPd [TA658].

B.2.9.2. IsaPd vs daratumumab monotherapy

In practice, clinicians have suggested that IsaPd and daratumumab are currently used in different patient populations (3). However, given daratumumab is now routinely available at 4th line and has been included as a comparator in the scope for this reappraisal, we have attempted to provide the committee with informative analyses comparing IsaPd and daratumumab monotherapy. Unfortunately, no data were identified that would allow an anchored indirect treatment comparison. As such, in line with Decision Support Unit (DSU) guidance (122) unanchored indirect comparison methods were considered. A matching adjusted indirect treatment comparison (MAIC) approach was chosen for the following reasons: (i) the outcomes of interest were time-to-event outcomes; (ii) there was overlap in the variables included in the adjustment; and (iii) multiple outcomes were assessed but only one comparison.

Two studies (ICARIA-MM and SIRIUS) were included in the unanchored MAIC analyses. The SIRIUS trial was also used as the primary trial-based data source for the appraisal of

daratumumab monotherapy [TA510] (118) and TA783 (5)). Description of the MAIC has been provided in Appendix P.

The limited sample size of the SIRIUS trial (n=106) and the 4th line subgroup of ICARIA-MM (n=110, n=52 in IsaPd arm), and the need to include all key prognostic factors while retaining suitable effective sample size (ESS) for the 4th line population, meant the ITT population from ICARIA-MM IsaPd arm had to be used in the MAIC.

However, despite using ICARIA-MM ITT population for the matching to SIRIUS, it was not possible to match on a sufficient number of prognostic factors while retaining suitable effective sample size. When all available characteristics are adjusted for, the resulting ESS was severely limited, n=5. When the MAIC was restricted to a subset of the variables that were considered most likely prognostic and/or effect modifiers, it resulted in an ESS of n=42 in the IsaPd arm; less than a third of the original sample size (IsaPd ITT=154). Using the ICARIA-MM ITT to match to SIRIUS (where most patients were 6th line+, median of 5 prior lines) also meant that the weighted population of patients in the IsaPd arm will, by definition, differ from the unweighted 4th line subgroup of the ICARIA-MM trial and no longer reflect the population relevant to the decision problem.

As a result of these limitations, the SACT data for daratumumab monotherapy and SACT data for IsaPd were considered the best available data to inform the economic model because it reflected outcomes for both treatments at 4th line in a UK population. Due to data limitations with SACT it was not possible to conduct a MAIC, however the approach of using SACT to inform decision making has been accepted in TA783 (daratumumab monotherapy vs Pd).

B.2.9.3. SACT datasets

Observational data were collected during the period of managed access via the SACT database (Section B.2.3.2 and Section B.2.6) for both IsaPd and daratumumab monotherapy.

The data collection period for IsaPd SACT (combined cohort) was from December 2019 to March 2022 (Section B.2.3.2), and the data collection period for daratumumab monotherapy was from January 2018 to November 2020. The SACT dataset provides a cohort of patients representative of clinical practice in England, with 737 patients being treated with IsaPd over 28 months. Similar data were available for daratumumab collected during the period of managed access via the SACT database, with 2,301 patients treated over 34 months. These

data are indicative of the real-world outcomes for IsaPd and daratumumab monotherapy; however, since individual patient data (IPD) are not available from SACT, it is only possible to conduct a naïve comparison between the IsaPd SACT and the daratumumab monotherapy SACT which is presented as an exploratory analysis.

Patient characteristics from SACT for both therapies are reported in Table 26. The median age of patients treated with IsaPd was not reported for the combined cohort (but was 71 and 66 years, in the EAMS and CDF cohorts respectively). The median age of patients receiving daratumumab was 71 years. Patients included in the SACT analysis were slightly older and had higher ECOG-PS scores than would be observed in clinical trials for both drugs, (5, 97, 108) as would be expected with real-world vs clinical trial populations, however there is a notable level of missing data for ECOG-PS in both datasets. Advisory board feedback from clinicians indicated that since the availability of IsaPd through the CDF, fewer patients receive daratumumab, with those patients that do typically being a specific subset with poorer prognosis (i.e. older age, frailer, poor ECOG-PS and low blood counts (e.g. neutrophil and platelet counts) (3). Some of these informative baseline characteristics (frailty, blood counts) which clinicians considered particularly important when determining the optimal treatment option for a patient at 4th line are not captured in the SACT dataset. Furthermore, any other unmeasured confounders such as comorbidities and prior therapies that can significantly differ between patients that received IsaPd vs daratumumab monotherapy remain a risk when considering this dataset for any comparisons.

Table 26. Patient characteristics IsaPd SACT and daratumumab SACT

N (%)	IsaPd (N=737)	Dara (N=2,301)
Sex		
Male	450 (61)	1,342 (58)
Female	287 (39)	959 (42)
Age		
Median (range)	NR†	71 (NR)
<40	5 (1)	4 (<1)
40-49	25 (3)	64 (3)
50-59	110 (15)	305 (13)
60-69	207 (28)	571 (25)
70-79	297 (40)	967 (42)
80+	93 (13)	390 (17)
ECOG-PS		
0	149 (20)	467 (20)
1	286 (39)	936 (41)
2	98 (13)	341 (15)
3	5 (1)	36 (2)
4	1 (<1)	1 (<1)
Missing	198 (27)	520 (23)

†Median age was not reported for the combined IsaPd SACT dataset – median age was reported for the separate CDF and EAMs cohorts: 71 and 66 years, in the EAMS and CDF cohorts, respectively.
Abbreviations: CDF, Cancer Drugs Fund; Dara, daratumumab; EAMS, Early Access to Medicines Scheme; ECOG-PS, Eastern Cooperative Oncology Score Performance Status; IsaPd, isatuximab + pomalidomide + dexamethasone; SACT, Systemic Anti-Cancer Therapy.

The IsaPd SACT subsequent therapies are reported in full in Table 24. A comparison of subsequent therapies for both daratumumab monotherapy and IsaPd in SACT is presented in Table 27. The daratumumab SACT contained a higher proportion of patients who subsequently received Pd vs IsaPd SACT (63.8% vs <2%, respectively), and a lower proportion who received PanVd (13.2% vs 46–57%, respectively). Advisory board feedback from expert myeloma clinicians suggests that the receipt of Pd as a subsequent therapy after daratumumab monotherapy at 4th line in the real-world could be benefiting these patients considerably, compared with patients who receive IsaPd at 4th line for whom there are currently no effective treatments options in subsequent lines of therapy (3). Patients who receive IsaPd would typically receive PanVd which they consider as having ‘poor clinical benefit’ or would be treated palliatively if they cannot enter a suitable clinical trial. This broadly aligns to the data observed in SACT for subsequent treatment received after SACT (Table 27) (3). It is highly likely that these differences in subsequent treatments impact survival estimates derived from the comparison, especially with newer interventions in development for 5th line+ with potential to improve longer term outcomes after either daratumumab monotherapy or IsaPd.

Table 27. Subsequent treatments accounting for ≥3% of all subsequent therapies†

Treatment, %	IsaPd (N=737)	Dara (N=1,111)
Belantamab mafodotin	13.8	–
Melphalan	8.5	–
Cyclophosphamide	6.4	–
Bortezomib	4.3	–
Melphalan + thalidomide	5.3	–
Pomalidomide	–	63.8
Bortezomib + Panobinostat	61.7	13.2
Cyclophosphamide + pomalidomide	–	5.0

†The first subsequent treatment after IsaPd and the following subsequent treatments across CDF and EAMS cohorts were pooled and reweighted to generate percentage use.
Abbreviations: CDF, Cancer Drugs Fund; Dara, daratumumab monotherapy; EAMS, Early Access to Medicines Scheme; IsaPd, isatuximab + pomalidomide + dexamethasone; SACT, Systemic Anti-Cancer Therapy.

Increased median treatment duration (considered a proxy for PFS) was observed for IsaPd (8.9 months [95% CI: 7.3, 10.8]) vs daratumumab monotherapy (4.5 months [95% CI: 4.3, 4.9]) in the naïve SACT comparison; showing a clear and statistically significant clinical benefit (no overlapping confidence intervals) for IsaPd ($p < 0.0001$). This finding was also observed for PFS in the MAIC vs daratumumab monotherapy (Appendix P).

An analysis was conducted that used digitised KM SACT data to model IsaPd and daratumumab monotherapy OS and treatment duration. The HRs and event numbers for the naïve comparison of IsaPd compared with daratumumab monotherapy for both OS and PFS are presented in Table 28. Note that compared with what was reported in the SACT reports for daratumumab and IsaPd, the event numbers for OS and treatment duration are not exact in our analyses. This is due to imperfections in the digitisation process from the available SACT curves, especially where there are large numbers of events. Although an exact match was not possible, the curves ultimately chosen were those with the closest number of events to the reported data. There was a larger discrepancy noted in the events generated after reconstruction of daratumumab monotherapy outcomes compared with IsaPd (1,387 events for daratumumab OS in SACT data vs 1,367 in reconstructed SACT data); however, this is most likely to have a positive effect on the daratumumab monotherapy arm (i.e. keeping more patients alive/on treatment with daratumumab) and therefore generate a conservative estimate of treatment effect for IsaPd vs daratumumab monotherapy.

The associated Kaplan-Meier plots, and number of patients at risk for IsaPd are presented in Section B.3.3.2.1 and Section B.3.3.2.2 and for daratumumab in Section B.3.3.2.2.

Table 28. Hazard ratios and event counts for comparison of isatuximab SACT and daratumumab SACT for OS and TTD

	OS	TTD
HR estimate, IsaPd vs daratumumab monotherapy	0.880	0.601
95% CI	0.777, 0.997	0.539, 0.671
P-value	0.0445	<0.0001
Isatuximab	N=736, Events=309	N=736, Events=390
Daratumumab	N=2,300, Events=1367	N=2300, Events=1,839

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; SACT, systemic anti-cancer therapy; TTD, time to discontinuation.

Naïve comparisons are by nature associated with risk of bias, given that no adjustment is made for differences in patient characteristics between the two data sources. A limitation of the SACT data is the availability of baseline characteristics, including the range of characteristics collected as well as missing data for collected baseline characteristics, e.g. ECOG-PS (27% missing data for IsaPd in SACT). Clinical experts have suggested that there are challenges in using ECOG-PS to assess performance status and that it is often not recorded or recorded inaccurately. The limited baseline data collected also make it difficult to characterise the patients receiving IsaPd and daratumumab in practice. The potential impact of subsequent therapies which differ between the two treatments may also confound outcomes. Feedback from the advisory board noted that the subsequent therapy data was broadly reflective of clinical practice, with two-thirds of patients going on to Pd after failing daratumumab monotherapy and the long half-life of daratumumab monotherapy may accentuate the effect of Pd if received as subsequent treatment (3). Conversely, they noted the current absence of effective treatments after IsaPd in UK clinical practice. However, clinical experts stated that a triplet combination (IsaPd) was the best available treatment option at 4th line for the majority of patients (3, 97) and that with newer interventions in development for 5th line+ this has the potential to improve longer term outcomes.

In addition, the data collection period for IsaPd SACT significantly overlapped with the COVID-19 pandemic which would have impacted the data due to changes in SACT prescribing. NHS England Interim COVID-19 guidelines allowed the use of oral Pd as 2nd or 3rd line therapy instead of IV treatments in patients who had been previously treated with lenalidomide (123, 124) to reduce the need for chemotherapy, reduce admissions and risk of neutropenia. Therefore, if patients had already received Pd, they would not be eligible for IsaPd at 4th line within the CDF. Furthermore, clinical experts noted extended dosing intervals, missed doses and in the first wave of the COVID-19 pandemic in particular,

suspending isatuximab and continuing patients on Pd to reduce the footfall in hospitals (3). This has implications for interpretation of SACT data for IsaPd.

Nevertheless, despite these limitations, the SACT data reflect UK practice at 4th line so is aligned to the decision problem and provides the most relevant evidence to allow a comparison between IsaPd and daratumumab monotherapy. An analysis utilising the SACT data has therefore been incorporated into the cost-effectiveness analysis (Section B.3.3.2.2).

B.2.10. Adverse reactions

B.2.10.1. ICARIA-MM

With three additional years of follow-up, the overall safety profile (safety set) remains consistent with what was reported in the original submission: the addition of isatuximab to Pd did not add substantial safety concerns. A detailed summary of safety outcomes (safety set) from the ICARIA-MM trial can be provided on request.

In the 4th line subgroup, at least one treatment emergent adverse event (TEAE) was reported in almost all the patients in both arms (100% and 98.3% in the IsaPd and Pd arms, respectively) (Table 29). While Grade ≥3 TEAEs were reported more frequently in the IsaPd arm than in the Pd arm (90.2% vs 74.1%), the incidence of Grade 5 (fatal) TEAEs was similar in both arms (9.8% and 10.3% in the IsaPd and Pd arms, respectively). A higher incidence of serious TEAEs was observed in the IsaPd arm than in the Pd arm (80.4% vs 58.6%). There were more serious treatment-related AEs in the IsaPd arm vs the Pd arm (39.2% vs 22.4%, respectively). Definitive treatment discontinuation due to TEAEs occurred infrequently and at a similar rate in both treatment arms (13.7% in the IsaPd arm and 19.0% in the Pd arm). Isatuximab was prematurely discontinued due to TEAE in four patients (2.0%) in the IsaPd arm.

Table 29. Overview of TEAEs (4th line safety population)

	Pd (N=58)	IsaPd (N=51)
Patients with any TEAE	57 (98.3)	51 (100)
Patients with any Grade ≥ 3 TEAE	43 (74.1)	46 (90.2)
Patients with any Grade 3-4 TEAE	42 (72.4)	45 (88.2)
Patients with any Grade 5 TEAE	6 (10.3)	5 (9.8)
Patients with any treatment emergent SAE†	34 (58.6)	41 (80.4)
Patients with any TEAE leading to definitive treatment discontinuation	11 (19.0)	7 (13.7)
Patients with any TEAE leading to premature discontinuation of:		
Isatuximab	NA	1 (2.0)
Pomalidomide	0	2 (3.9)
Dexamethasone	2 (3.4)	2 (3.9)
Patients with any AESI‡	0	5 (9.8)
Patients with any IR of grade ≥ 3	0	1 (2.0)
Patients with any treatment-related TEAE¶ (any grade)	45 (77.6)	45 (88.2)
Patients with any treatment-related grade ≥ 3 TEAE	29 (50.0)	36 (70.6)
Patients with any serious treatment-related TEAE	13 (22.4)	20 (39.2)

Source: Sanofi, Clinical study report fourth-line analysis, data on file (2022) (87).
Notes: † 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; Abbreviations: IsaPd, Isatuximab + pomalidomide + dexamethasone; NA, Not applicable; Pd, pomalidomide + dexamethasone; TEAE, treatment emergent adverse event.

B.2.11. Ongoing studies

The IONA-MM study, a multinational observational study assessing isatuximab in different combinations (IsaPd, IsaKd, or other Isa regimens) in patients with RRMM in routine clinical practice, is currently ongoing (125). Results are expected early 2026.

B.2.12. Interpretation of clinical effectiveness and safety evidence

B.2.12.1. Principal findings from clinical evidence, uncertainties and applicability of evidence to the UK

ICARIA-MM is a robustly-designed phase 3 RCT, with a population that closely reflects the real-world patient population eligible for treatment with IsaPd, and is the only RCT evaluating IsaPd in RRMM. Within this submission, an additional ~3 years of OS data are provided relative to the original company submission for TA653, demonstrating that the efficacy benefits of IsaPd are maintained long term.

The long term ICARIA-MM data demonstrated that in the 4th line population, IsaPd provided a statistically significant PFS benefit over the trial comparator, Pd, with a median PFS improvement of 5.87 months. In addition, IsaPd demonstrated a clinically meaningful

improvement in OS, with a median improvement of 15.57 months vs Pd (not statistically significant).

Due to differences between the two treatment arms in ICARIA-MM in terms of subsequent therapies and in particular the higher use of daratumumab in the Pd arm as subsequent therapy, the treatment effect estimate for OS may be impacted. During the advisory board, clinicians highlighted that in the Pd arm of the ICARIA-MM trial, patients were naïve to daratumumab, so a large proportion (41.1%) received daratumumab as subsequent therapy. Although there are several interventions in the list of subsequent treatments that would not be used in the UK, the distributions were considered comparable between treatment arms, with the exception of daratumumab after progression in the Pd arm (3). Sensitivity analyses have therefore attempted to adjust for receipt of daratumumab as subsequent therapy in both arms using methods recommended in NICE DSU TSD16 (126). Using the IPCW and TSE methods to remove the impact on OS of receiving daratumumab post progression had minimal but positive overall impact on the relative treatment effect of IsaPd vs Pd (IPCW HR:0.650 [95% CI: 0.373, 1.132]; TSE HR: 0.618 [95% CI: 0.378 – 1.009) (Section B.2.6.1.2.1. p62, and Appendix N). The base case model uses the protocol specified OS HR for 4th line population directly from the trial, which may be considered a conservative estimate of treatment effect. The adjusted HRs removing the impact of daratumumab (IPCW and TSE) have nevertheless been tested in scenario analyses.

Although an exploratory endpoint involving a small number of patients, only patients treated in the IsaPd arm (both ITT and 4th-line populations) achieved MRD negativity at each sensitivity level (10^{-4}, 10^{-5}, and 10^{-6}), compared with no patients in the Pd arm. MRD represents a more sensitive measure of disease burden than conventional complete response and has been recently accepted in other appraisals in myeloma as a marker of long term outcomes (127), and therefore further highlights the deep responses and efficacy of this triplet combination in a relapsed and refractory patient population.

Quality-of-life as measured by EQ-5D-5L HSUV and EQ-5D-5L VAS scores were sustained over time and similar in both treatment groups, in patients at 4th line of treatment. Taken together, the outcomes reported for ICARIA-MM demonstrate the clinical efficacy and safety of IsaPd in the 4th line population with longer follow up.

B.2.12.2. IsaPd SACT

Following the previous appraisal, SACT observational data from patients receiving IsaPd via the CDF or EAMS was collected. In total, 737 patients received IsaPd through the CDF and

EAMS programmes between 2nd December 2019 and 31st March 2022. PFS data is not collected in the SACT dataset, nevertheless median treatment duration (which can be considered a proxy for PFS) for all patients was 8.9 months and comparable with TTD in the 4th line population (median [redacted]), which highlights the benefit conferred in terms of disease control to patients in England who accessed IsaPd in the real-world clinical setting. Of note is that the period in which IsaPd data was collected in SACT significantly overlapped the period of the COVID-19 pandemic (2nd December 2019 to 31st March 2022), where clinicians noted that some patients received an attenuated dose or missed doses of isatuximab whilst therapy with pomalidomide and dexamethasone (both given orally) were continued during the pandemic. This may have diluted the treatment effect and duration seen with IsaPd in the SACT dataset. Furthermore, where patients had already received Pd (following the interim treatment changes guidelines during COVID-19), they could not receive IsaPd. Although the median OS in SACT was 18.8 months (95% CI: 15.7, 22.9), the follow up was short (minimum follow-up of 4.8 months, and a median follow-up of 9.4 months) and 58% of patients were censored for an OS event in the IsaPd SACT data (n=425/736[f] patients with data). Experts agreed that with longer follow-up, the outcomes with IsaPd may improve. This difference in OS between the trial and RWE may in part be explained by differences in the baseline characteristics of the two datasets; clinical experts highlighted the large amount of missing ECOG-PS data, poorer ECOG-PS where it was captured, and the older age of patients in the SACT dataset compared with the ICARIA-MM trial identified as a potential factor driving this difference. It was also noted that the data collected in SACT did not report blood counts (neutrophil counts, platelet counts), co-morbidities, and transfusion requirements. These characteristics are often used to inform whether a patient should receive IsaPd or other alternative treatments at 4th line. Without these characteristics, clinicians stated it was difficult to accurately characterise the patients. Overall, the shorter OS reported in the real-world were not deemed by experts as altogether surprising given that patients in clinical practice are heterogenous and unlikely to meet stringent eligibility criteria that would be applied in a trial setting.

[f] One patient died on the same day they started treatment, and as such, they were excluded from the model as their treatment duration was 0 days.

B.2.12.3. IsaPd vs daratumumab monotherapy

No head-to-head data were identified to compare IsaPd vs daratumumab monotherapy and as such, a naïve comparison of the IsaPd SACT vs daratumumab SACT data was deemed to be most relevant, informative and aligned to the decision problem of this appraisal.

The available SACT data for IsaPd and daratumumab monotherapy has the advantage that it only includes 4th line patients in the English setting. However, the data collection period for daratumumab monotherapy in SACT had minimal overlap with the data collection period for IsaPd (especially the CDF cohort). In clinical practice, patients receiving daratumumab monotherapy now likely differ from those receiving IsaPd (and those that received daratumumab monotherapy during the SACT period), with clinical experts explaining that daratumumab monotherapy is often offered to patients who are not fit enough to tolerate a triplet regimen, since IsaPd became available (3). Furthermore, due to its naïve nature, this comparison should be interpreted with caution and is considered exploratory.

The SACT dataset provides a patient cohort representative of clinical practice in England, with 737 patients being treated with IsaPd over 28 months in the combined cohort. Similar data were available for daratumumab, collected during the period of managed access via the SACT database, with 2,301 patients treated over 34 months. This naïve comparison continued to demonstrate increased median treatment duration for IsaPd (considered a proxy for PFS) (8.9 months [95% CI: 7.3, 10.8]) than that observed for daratumumab monotherapy (4.5 months [95% CI: 4.3, 4.9]), showing a clear clinical benefit for IsaPd compared to daratumumab monotherapy for an outcome that is clearly important to people living with multiple myeloma (128, 129).

Any potential benefits to OS are not as clear as this outcome is likely to be confounded by the differences in baseline characteristics of patient population receiving these treatments, their prior therapies, prognosis at progression and particularly subsequent therapies received after these treatments were provided within the CDF. This naïve analysis has its limitations, including the limited baseline characteristic data available from SACT, inability to adjust for differences in patient population data recorded, significant missing data, and the potential impact of subsequent therapies which differed between the two treatments. Clinical advisory board feedback suggests that the receipt of Pd as subsequent therapy after daratumumab in the real-world could be benefiting the patients in the daratumumab arm vs patients receiving predominantly PanVd after IsaPd, which they consider as having ‘poor clinical benefit’ (3). The data collection period for SACT also coincided with the COVID-19 pandemic for both therapies, but more so for IsaPd, which would have impacted the use of

IsaPd, the collection of data and may also have implications for interpretation of the data. Clinical experts noted extended dosing intervals, missed doses, and in the first wave of the COVID-19 pandemic, suspending isatuximab and continuing patients on Pd to reduce the footfall in hospitals. Nevertheless, the continued uptake over the short period of time was considered by clinicians indicative of the need for the triplet combination (IsaPd) in 4th line (3).

B.2.12.4. Clinical experience during CDF with IsaPd

Following the previous submission, the availability of IsaPd to patients and clinicians via the CDF was favourably received (3). The evidence presented in this submission highlights that IsaPd has a higher response rate which last longer than other available treatment options at this line of therapy. As highlighted in Section B.1.3.4.3, if IsaPd was not available as a treatment option, SoC therapy (e.g. Pd or daratumumab monotherapy) would be the most likely option. Currently, SoC therapy is associated with lower response rates, shorter duration of response and poorer PFS outcomes compared with IsaPd. Clinicians opt to use the treatment which offers the longest period of PFS (3), an outcome that is highly valued by end-stage patients- reflected in the sustained uptake of IsaPd in the CDF, despite the availability of daratumumab monotherapy and Pd.

B.2.12.5. Summary

Overall, the 3 years of additional data from ICARIA-MM confirm the treatment benefit associated with IsaPd. Whilst immature in terms of OS data, the available SACT data for IsaPd also corroborates the treatment duration/PFS observed in ICARIA-MM. IsaPd confers a longer PFS than other available treatments at 4th line and therefore maximises a patient's potential to be able to benefit from 5th line therapies that are available, both now and in the future, to further extend OS. IsaPd at 4th line allows patients to access treatment with an anti-CD38 plus the Pd backbone without the risk of inferior sequential treatment response and increased patient attrition between lines of treatment. As an increasingly preferred triplet therapy available at 4th line (3), IsaPd clearly addresses a continued unmet need which is evidenced by the rapid and sustained uptake observed in the NHS whilst available via the CDF.

B.3. Cost effectiveness

A cost-utility analysis was conducted to evaluate the cost-effectiveness of IsaPd vs comparators from the UK NHS perspective and considered RRMM patients who have received three prior lines of therapy, including lenalidomide and a proteasome inhibitor (PI) (4th line)

- A partitioned survival model (PSM) was used, a lifetime horizon was applied, and costs and benefits were discounted at 3.5% per annum
- Key clinical uncertainties during the original Company submission were addressed with more mature OS, PFS and time on treatment data, systematic anti-cancer therapy (SACT) data and exploratory treatment switching analyses to remove the effect of daratumumab as subsequent therapy

To inform the clinical inputs in both arms for the comparison of IsaPd with Pd, outcomes from the ICARIA-MM 4th line trial were used directly and utility values were based on EQ-5D-5L values from ICARIA-MM mapped to EQ-5D-3L as per the NICE reference case

In the base-case analysis (isatuximab Patient Access Scheme [PAS] price only and no comparator discounts), IsaPd is associated with an incremental cost of £184,947 and incremental quality-adjusted life years (QALYs) of 1.12 compared with Pd, resulting in an incremental cost-effectiveness ratio (ICER) of £165,554/QALY

- Sensitivity/scenario analyses supporting the base-case analyses vs Pd are robust, with key scenarios using plausible alternative survival distributions resulting in minimal changes to the ICER and subsequent treatment adjustments suggesting some improvement in the ICER compared to base case.

A naïve comparison was considered against daratumumab monotherapy where data from SACT database was used to inform clinical inputs for both IsaPd and daratumumab monotherapy

- In this analysis (isatuximab PAS price only and no comparator discounts), IsaPd is associated with an incremental cost of [redacted] and incremental QALYs of [redacted] compared with daratumumab, resulting in an ICER of £144,981/QALY.

All ICERs reported include a discount to isatuximab only, all other treatments are at list price and so do not reflect true cost-effectiveness.

This appraisal continues to highlight the inherent challenges in demonstrating cost-effectiveness of branded combination oncology products where the combination leads to better outcomes vs the comparators which are priced to the NICE acceptability thresholds.

- Using the standard NICE reference case, IsaPd is likely not cost-effective at £0 for isatuximab
- Non-reference case analyses that consider the removal of high-cost background non-cost-effective care (Pd) and patent expiry for pomalidomide (expected in Q2 2024) demonstrate that IsaPd can be considered a cost-effective use of NHS resources at a WTP of £50,000/QALY
- Applying a value attribution framework confirms that isatuximab is available to the NHS at a value-based price.

The approved PAS, [redacted] and the dwindling patient pool eligible for anti-CD38 treatments at 4th line mean that a recommendation for IsaPd is associated with a low budgetary impact and therefore constitutes a short-term and low risk decision.

B.3.1. Published cost-effectiveness studies

A broad SLR was conducted to identify cost-effectiveness studies of treatments for patients with RRMM from the published literature. A detailed description of the review methods, full results and quality assessment of the identified studies are reported in Appendix G.

In the original SLR (October 2018), a total of 20 studies (reported in 27 publications) were included in the review. The original search was updated in June 2019 from which no additional studies were included. In the update search (November 2022), a total of four studies (reported in seven publications), were included in the review. Taken together, a total of 34 publications (1, 5, 26, 55, 77, 78, 102, 112, 118, 130-154) were included across the de novo SLR and SLR update, reporting on 24 unique trials.

Most of the included studies used a cost-utility approach with QALYs as the primary outcome measure. The use of modelling with a lifetime horizon is a key strength of the majority of the studies. The studies used very similar models, generally based on health states that followed the progression of the disease. Survival curves were selected to extrapolate short-term data taken from RCTs, to the long-term and often represented a key assumption of the model. The use of detailed stochastic analysis was another strength of many of the studies. NICE HTAs provided useful extensive details around model structure, data inputs, methods to synthesise clinical efficacy, survival curve extrapolation scenarios and methods to deal with uncertainty.

Aligned with the decision problem, the cost effectiveness evidence submitted is focused on comparators relevant for people who have had three prior therapies only (4th line). The comparators considered in the submission are Pd, and daratumumab monotherapy as an exploratory analysis. A total of eight studies (reported in 12 publications) (1, 5, 26, 55, 77, 78, 112, 118, 130, 152-154) were relevant to the NICE decision problem for this reappraisal. 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] (55, 78), and daratumumab monotherapy [TA510, TA783] (5, 77, 112, 118) have been used to inform some model inputs, as both Pd and daratumumab monotherapy have been recommended by NICE as treatment options for 4th line. Features of the economic analyses of these TAs are summarised in Section B.3.2.3 and Appendix G.

B.3.2. Economic analysis

A de novo cost-effectiveness model (CEM) for IsaPd in RRMM was developed to support the original company submission to NICE [TA658]. For this resubmission, the CEM has been adapted to include an updated data cut (cut-off date 14 March 2022 for PFS / 27 January 2022 for OS) from the Phase 3 trial ICARIA-MM, contributing a further three years of follow up data.

As indicated in Section B.1.1, the scope of Review of TA658 [ID4067] has undergone significant and unanticipated changes and has fundamentally disadvantaged IsaPd in an appraisal that was already challenging due to the nature of being a branded combination therapy, where the backbone therapy Pd has already been priced to meet the £50,000/QALY threshold. To satisfy the requirements of the re-issued NICE scope for this Review of TA658, whilst Sanofi has tried to provide informative analyses for a comparison vs daratumumab monotherapy, they are considered exploratory due to its naïve nature and the utilisation of RWE collected from SACT in England for both therapies; despite clinical opinion that these treatments would now be used in different patient populations. Hence any comparative analysis vs daratumumab monotherapy should be interpreted with caution.

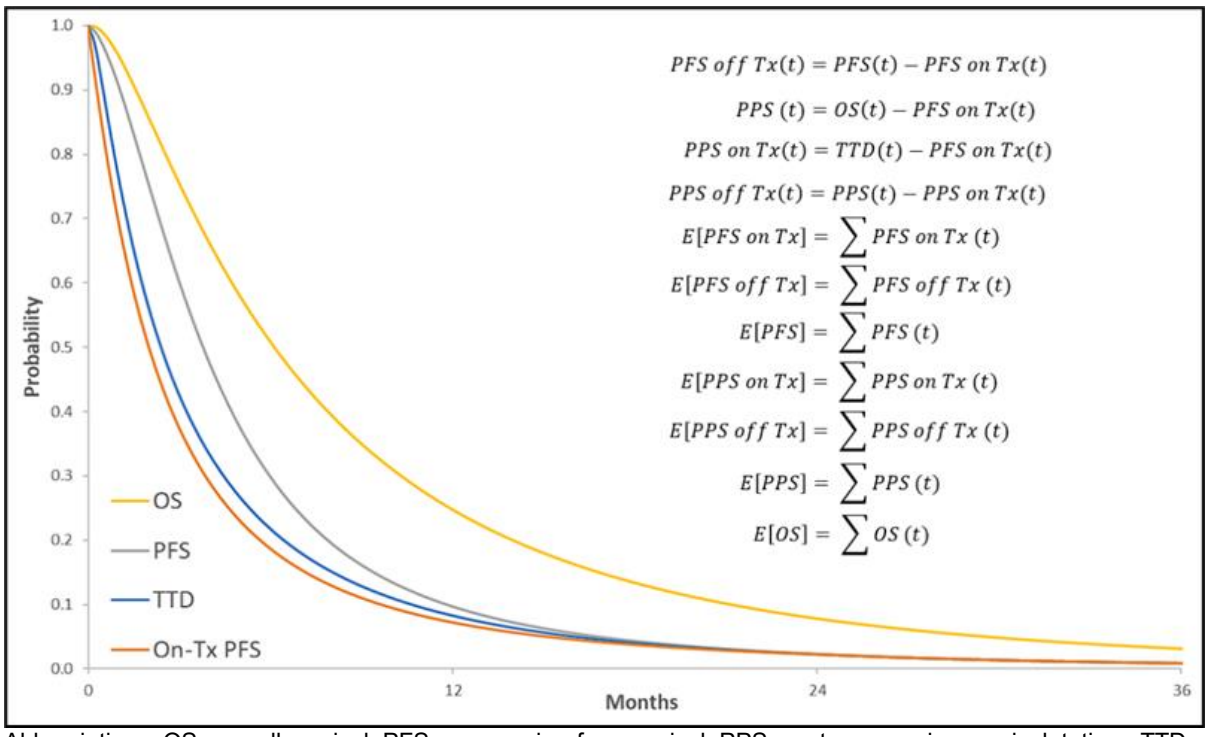
B.3.2.1. Patient population

The population in the model base case is the subgroup of patients from the ICARIA-MM trial who have received a median of three prior lines of therapy (4th line), including lenalidomide and a PI. As per the original company submission, in England and Wales, it is anticipated that IsaPd will continue to be used in patients at 4th line therapy (Section B.1.1).

B.3.2.2. Model structure

A partitioned survival model (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 other treatments. A simplified schematic of the model is shown in Figure 8.

Figure 8. Simple schematic of the partitioned survival model



Abbreviations: OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; t, time; TTD, time to discontinuation; Tx; treatment.

While a three-state model (PFS, PPS, dead) is more conventionally used in economic models of oncology therapeutics, a five-state model (PFS on/off treatment, PPS on/off treatment, dead) was used in this instance to allow for the possibility that patients might stop therapy prior to disease progression and for utility values and follow-up and monitoring costs to differ for patients who are on and off treatment in the progression-free and post-progression states. For this NICE submission, based on the feedback from EAG during TA658 appraisal, the utility values have not been varied based on whether patients are on or off treatment (Section B.3.4.4). Costs of comparator medications and medication administration are calculated based on distributions for TTD rather than PFS on treatment, which is reflective of the delay between assessment of progression and cessation of study drugs as observed in ICARIA-MM. To account for the fact that most patients continue onto other lines of treatment after progression, the model also allows for the possibility to include "one-off" incremental costs assigned at the point of progression to reflect incremental effects of subsequent treatments received post-progression. These incremental effects on costs are calculated by multiplying the average duration of individual post progression therapies by the costs of the relevant subsequent therapy medications. The PFS on treatment distribution is constrained to be no greater than the TTD distribution to ensure that the model does not assign benefits of treatment to patients who are estimated to be off treatment for the purpose of costing. As such, PPS on treatment is assumed to be represented by the difference

between the TTD and PFS on treatment curves. The TTD, PFS, and PFS on treatment distributions are also constrained to be no greater than OS.

It was further assumed that the probability of death in any given model cycle implied by the OS distribution could not be less than that for the age- and sex-matched general population. This is implemented by deriving the probability of death from the OS distribution and checking this value against the corresponding general population probability and then applying to the survival probability in the prior cycle the greater of the two values. Accordingly, when the model projected probability of death is less than the general population mortality, the modelling of OS is in effect using a Markov approach (wherein transition probabilities are modelled explicitly) rather than a PSM.

B.3.2.2.1. Model structure selection and rationale

The modelling approach used in prior published economic evaluations of RRMM and guidance by the NICE DSU on the use of PSMs (155) were considered when selecting the modelling approach.

PSMs have been used extensively in economic evaluations in RRMM including the models used in the manufacturers' submissions to NICE for TA510/TA783 of daratumumab monotherapy (5, 77, 112, 118) and TA338/TA427 of Pd (55, 78). A PSM can directly use key primary and secondary trial outcomes such TTD, PFS, and OS to estimate model transitions.

The economic modelling approach was validated by clinical experts during the original NICE submission. Furthermore, the EAG and the committee accepted the PSM structure during the original appraisal of IsaPd [TA658] (26).

B.3.2.3. Features of the economic analysis

Key features of the economic analysis are outlined in Table 30.

Table 30. Features of the current economic analysis relative to previous NICE appraisals in RRMM

Factor	Previous appraisals				Original appraisal	Current appraisal [Review of TA658] [ID4067]	
	TA380 (Panobinostat)	TA427 (Pomalidomide)	TA510 (Daratumumab)	TA783 (Daratumumab-CDF review)	TA653 (IsaPd original appraisal)	Chosen values	Justification
Model type	CUA	CUA	CUA	CUA	CUA	CUA	NICE reference case
Time horizon	25 years (lifetime)	15 years (lifetime)	15 years (lifetime)	15 years (lifetime)	15 years (lifetime) Following ERG report, the time horizon was extended to 20 years to fully capture benefits for IsaPd.	40 years (lifetime)	NICE reference case recommends a lifetime horizon to capture all expected differences in costs and benefits. Implementation of the QALY shortfall calculations into the updated model necessitated the expansion of the model's maximum time horizon to a sufficient amount such that QALYs could be calculated for an entire lifetime for a person without multiple myeloma. To this end, the maximum time horizon was expanded to 40 years, which was deemed sufficient due to the advanced age of the model population (65.1 years). In the current base case only a small proportion of patients are alive in both arms after 20 years, accordingly a time horizon of 20 years has been tested in scenario analysis to test the impact on the ICER
Model cycle length	3 weeks	1 week	1 week	1 week	1 week	Years 0–20: 1 week Years 20–40: 1 year	Accounts for the different dosing schedules for treatments being compared. Majority of costs and outcomes are captured within the 20-year time horizon.

Factor	Previous appraisals				Original appraisal	Current appraisal [Review of TA658] [ID4067]	
	TA380 (Panobinostat)	**TA427 (Pomalidomide)**	**TA510 (Daratumumab)**	**TA783 (Daratumumab-CDF review)**	**TA653 (IsaPd original appraisal)**	**Chosen values**	**Justification**
Half cycle correction	Yes	No	No	No	No	Years 0–20: No Years 20–40: Yes	Years 0-20: Short cycle length (1 week) does not require half cycle correction. Years 20-40: Half cycle correction is applied for yearly cycle length.
Source of utilities	Trial based EORTC-30 mapped to EQ-5D	Utility scores were taken from the TMM1 trial	Utility scores were taken from the MM-003 trial.	Utility scores were mainly taken from the MM-003 trial.	EQ-5D-5L from ICARIA-MM trial mapped to EQ-5D-3L for IsaPd and Pd	EQ-5D-5L from ICARIA-MM trial mapped to EQ-5D-3L for IsaPd and Pd	A per NICE reference case and original Company submission.
Source of resource use	Resource use data came from clinical trials and UK studies	Resource use were taken from patient level data of the TMM1 trial and from several other published studies.	Resource use data came from clinical trials and UK studies	Resource use was taken TA338), from experts' opinion and from the pivotal RCTs.	Resource use was informed by daratumumab submission [TA510] and validated with UK expert opinion	Resource use were informed by daratumumab submission [TA510] and validated with UK expert opinion as part of the initial submission for IsaPd [TA658], costs inflated where relevant using PSSRU	As per original Company submission.
Source of 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	NHS reference costs, BNF, and eMIT	A per NICE reference case and original Company submission.

Abbreviations: BNF, British National Formulary; CUA, cost utility analysis; eMIT, electronic marketing information tool; MIMs, Monthly Index of Medical Specialities; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; UK, United Kingdom.

B.3.2.3.1. Perspective

The perspective considered is that of the NHS and Personal Social Services (PSS) in England and Wales, in line with current NICE guidelines.

B.3.2.3.2. Time horizon

A lifetime horizon was adopted in the analysis to adequately capture the differences in costs and outcomes between treatment arms over the lifetime of patients. A 40-year time horizon (with maximum age of 100 years) for the model allows explicit calculation of lifetime survival which is required for the calculation of QALY weights to implement a severity modifier (NICE manual 2022) (85), however most of the costs and outcomes are captured within the first 20 years in the base case and therefore a scenario analysis was tested considering a lifetime horizon of 20 years.

B.3.2.3.3. Cycle length and half-cycle correction

The model adopts a weekly cycle length from years 0 to 20 to permit accurate representation of the dosing regimens for IsaPd, Pd, and daratumumab. From 20 to 40 years a yearly cycle length is adopted as the majority of costs and outcomes are captured prior to 20 years. A half-cycle correction is therefore applied from year 20 onwards in the model.

B.3.2.3.4. Discounting

An annual discount rate of 3.5% is modelled for costs and outcomes in line with the NICE reference case and applied from the second year of the modelled time horizon (85). In scenario analysis, 1.5% discount rate for health effects and costs were tested.

B.3.2.4. Intervention technology and comparators

B.3.2.4.1. Intervention

The intervention considered is IsaPd, with dosing modelled as per ICARIA-MM:

- Isatuximab (IV): 10 mg/kg on days 1, 8, 15 and 22 of 28-day cycle 1 and days 1 and 15 for each subsequent 28-day cycle,
- Pomalidomide (Oral): 4 mg on days 1–21 of each 28-day cycle,

- Dexamethasone (Oral or IV if oral route could not be used): 40 mg (or 20 mg if the patient is ≥75 years old) on days 1, 8, 15 and 22 of each 28-day cycle.
    - 13.5% of patients received the 20mg oral dose and 25.5% of patients received treatment via IV in the IsaPd arm of ICARIA-MM

A scenario is presented where isatuximab is taken as a subcutaneous injection, as per the Quach 2022 study (156). A subcutaneous formulation for isatuximab is currently being studied in clinical trial in combination with Pd with anticipated primary completion in 2024, therefore a scenario has been included to demonstrate the impact of its availability on the incremental cost-effectiveness ratio (ICER). Patients received isatuximab via 1,400 mg injection on days 1, 8, 15 and 22 of 28-day Cycle 1 and days 1 and 15 for each subsequent 28-day cycle.

B.3.2.4.1.1. Isatuximab pre-medication

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

- Dexamethasone 40 mg orally or IV (or 20 mg oral or IV for patients ≥75 years of age),
- Acetaminophen (paracetamol) 650 mg to 1000 mg orally (or equivalent),
- Diphenhydramine 25 mg to 50 mg IV or orally (or equivalent [e.g. cetirizine, promethazine, dexchlorpheniramine]). The IV route is preferred for at least the first four 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.3.2.4.2. Comparators

Pd (as per ICARIA-MM)

- Pomalidomide (Oral): 4 mg on days 1–21 of each 28-day cycle,
- Dexamethasone (Oral or IV): 40 mg (or 20 mg if the patient is ≥75 years old) on days 1, 8, 15 and 22 of each 28-day cycle

- 15.5% of patients received the 20mg dose and 0% of patients received treatment via IV in the Pd arm of ICARIA-MM

As discussed in Section B.1.1 an exploratory analysis vs daratumumab monotherapy is also provided.

- Daratumumab monotherapy (as per the European Medicines Agency [EMA] (157))
    - 1,800 mg injection every week for each 28-day cycle for Cycles 1–2,
    - 1,800 mg injection every two weeks for each 28-day cycle for Cycles 3–6,
    - 1,800 mg injection every four weeks for each 28-day cycle for Cycles 7+.

In line with TA783, and as validated by clinical expert opinion, daratumumab is assumed to be administered as a subcutaneous injection in the majority of cases in clinical practice (3, 5, 77). A scenario where daratumumab is administered fully as IV has also been tested as per the SmPC, clinicians noted that in a minority of patients with significant tissue oedema daratumumab may be administered as IV:

Patients receive daratumumab 16 mg/kg infusion on days 1, 8, 15 and 22 of each cycle in Cycles 1–2, then days 1 and 15 of each cycle in Cycles 3–6, then day 1 of each cycle for subsequent cycle

B.3.3. Clinical parameters and variables

Patient level data from ICARIA-MM were used to inform the clinical inputs for IsaPd and Pd including TTD, PFS on-treatment, PFS, and OS. As a RCT, ICARIA-MM is the most robust evidence base for the comparison of IsaPd with Pd.

B.3.3.1. Patient characteristics

Patient baseline characteristics were derived from the 4th line subgroup of ICARIA-MM. A summary of the baseline characteristics used in the model are presented in Table 31. Although the patients entering the model are younger than those treated in the CDF, evidence from ICARIA-MM has demonstrated consistent outcomes across all pre-specified subgroups including age (<75 years vs ≥ 75 years) (Appendix E). Outcomes for age subgroups were not available from SACT.

Table 31. Baseline characteristics used in the economic model

Variable	Model input
Age (years)	65.1
Percentage male (%)	51.8%
Weight (kg)	73.1
BSA (m^2)	1.8

Abbreviations: BSA, body surface area.

B.3.3.2. Survival extrapolations

B.3.3.2.1. IsaPd and Pd survival extrapolation

Estimates of OS, PFS, PFS on treatment, TTD for IsaPd and Pd were derived by fitting parametric survival distributions to the individual patient data from ICARIA-MM in the 4th line population.

Standard parametric survival analysis consisted of fitting parametric distributions (including exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised gamma distributions) to the observed data from ICARIA-MM using two alternative approaches for parameterising the effect of treatment on PFS times:

“Restricted” (R) models in which a single parameter of the survival distribution is allowed to differ between groups; and

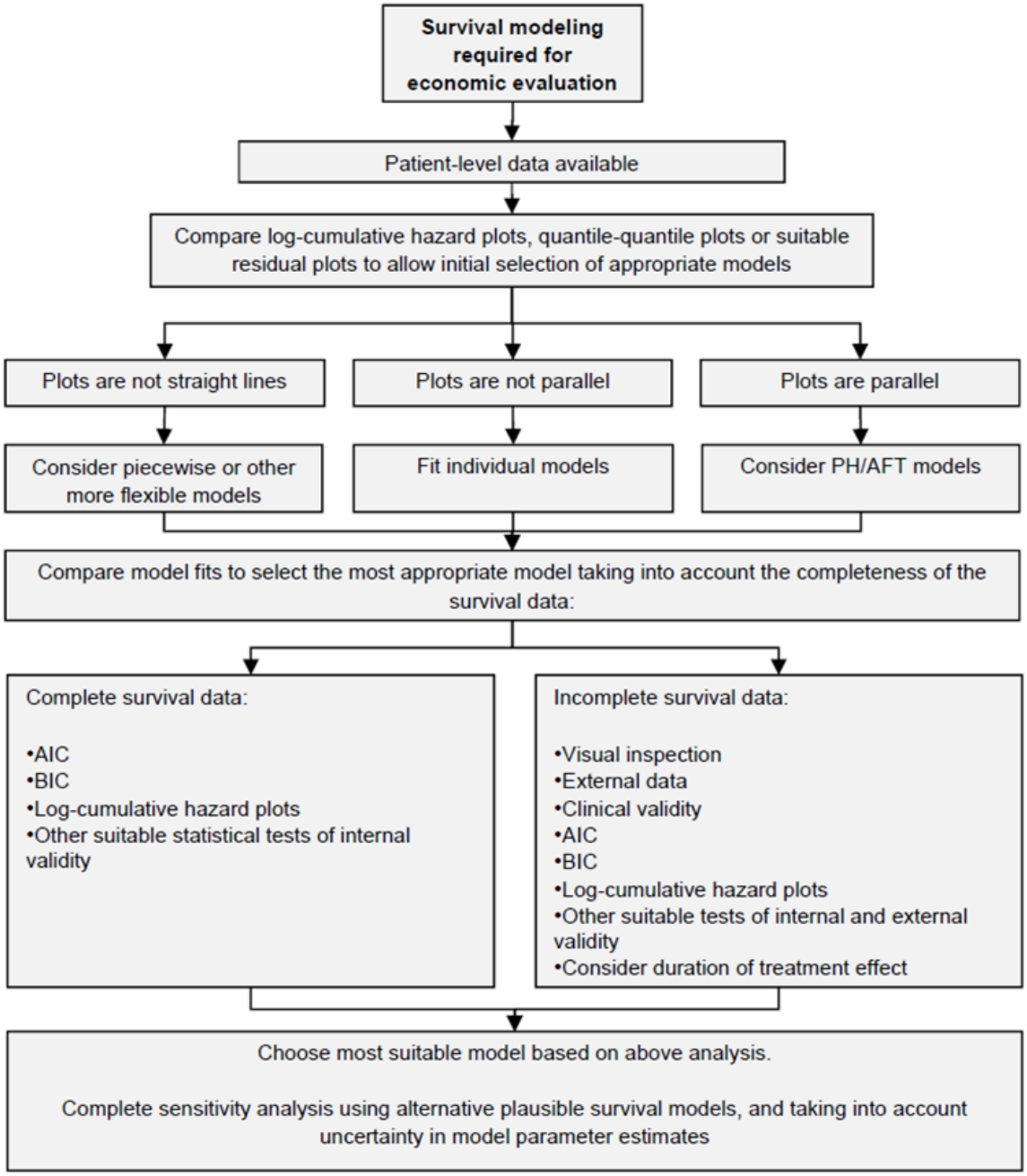
“Unrestricted” (U) models in which all parameters of the survival distribution are allowed to differ between groups

With both approaches, the distributions of survival for the treatment and control groups are assumed to be of the same type of distribution (e.g. both are Weibull). However, with the first approach (restricted models), in which the effect of treatment is restricted to a single distributional parameter (e.g. the scale parameter of the Weibull distribution), projections of survival are consistent with the proportional hazards (PH) assumption, accelerated failure time (AFT), or other univariate treatment effect models, depending on the underlying distribution (e.g. the Gompertz is a PH model, the lognormal and log-logistic are AFT models, and the exponential and Weibull are both PH and AFT models). The second approach (unrestricted models) places no such restrictions on the distributional parameters or the assumed nature of treatment effect within the class of distributions. Restricted cubic spline (RCS) models were also estimated, which used a single knot (in addition to the two boundary knots, which are always included). The boundary knots were based on the minimum and maximum failure times. The non-boundary knots were based on the median of

the failure times. As RRMM remains incurable, mixture and non-mixture cure models were not considered.

Selection of the most appropriate parametric model was assessed using goodness of fit statistics, visual inspection of survival distributions, hazard functions, and diagnostic plots for treatment effects, as well as clinical plausibility, as per NICE DSU TSD 14 (158) (Figure 9).

Figure 9. NICE DSU - selection process algorithm



Abbreviations: AFT, accelerated failure time; AIC, Akaike information criteria; BIC, Bayesian information criteria; DSU, Decision Support Unit; NICE, National Institute for Health and Care Excellence; PH, proportional hazard.

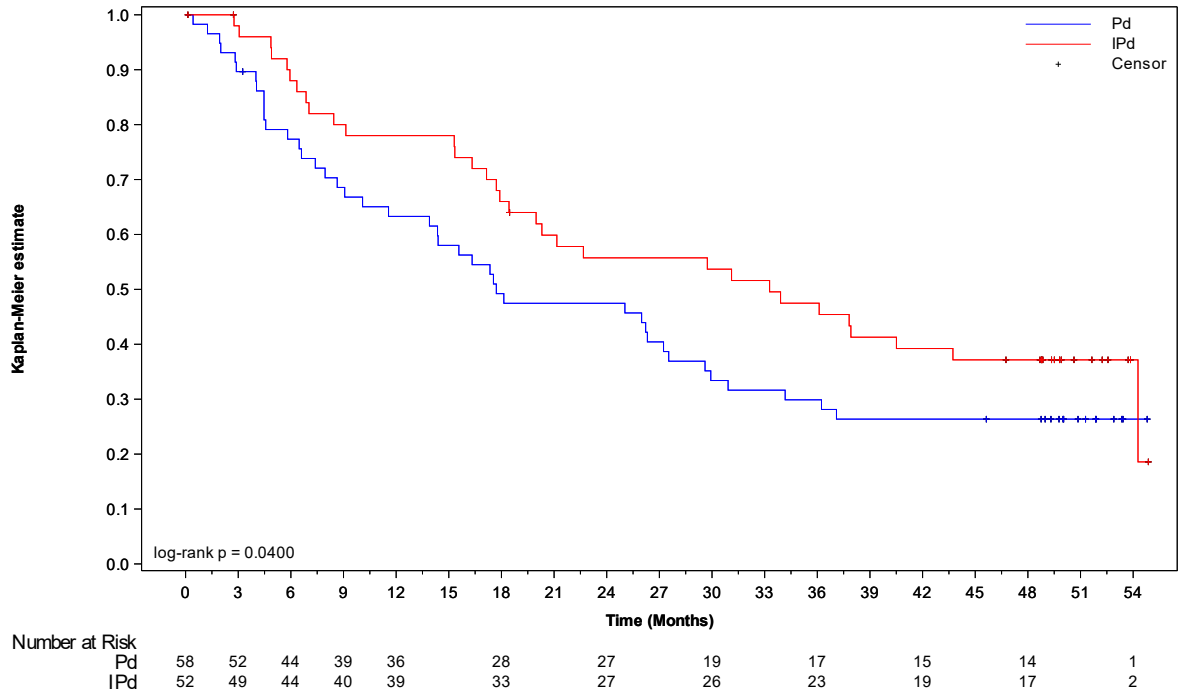
The Bayesian information criterion (BIC) was used as the primary measure of statistical fit, as it places a high penalty relative to other criteria, such as Akaike information criteria (AIC), on the number of parameters included in the distribution and hence avoids placing undue influence on the tail of the distribution which can have a large effect on long-term survival projections. The standard parametric survival analyses followed the approach outlined in the NICE DSU TSD 14 (158).

The use of two different survival distribution families for the two treatment arms of ICARIA-MM (e.g. a Weibull distribution for IsaPd and a log-logistic distribution for Pd) was not considered in the base case. However, given that in the previous appraisal the EAG accepted that the use of two different survival distribution families may be considered appropriate for IsaPd and Pd, the impact of this assumption has been tested in scenario analysis. Given that this is a comparison of a doublet vs a triplet therapy that includes a drug with a different mechanism of action, it would not be unexpected for them to follow different survival distributions.

B.3.3.2.1.1. Overall survival

At the final analysis of OS, a strong trend in OS benefit (stratified HR: 0.657; 95% CI: 0.409, 1.055) with a 15.57-month improvement in median OS, was observed with the addition of isatuximab to Pd treatment in the 4th line population. Median OS was 33.28 months (95% CI: 18.43, 54.28) in the IsaPd arm and 17.71 months (95% CI: 11.57, 27.53) in the Pd arm in the 4th line only subgroup. OS KM data for IsaPd and Pd for the 4th line population are presented in Figure 10.

Figure 10. OS KM, 4th line subgroup

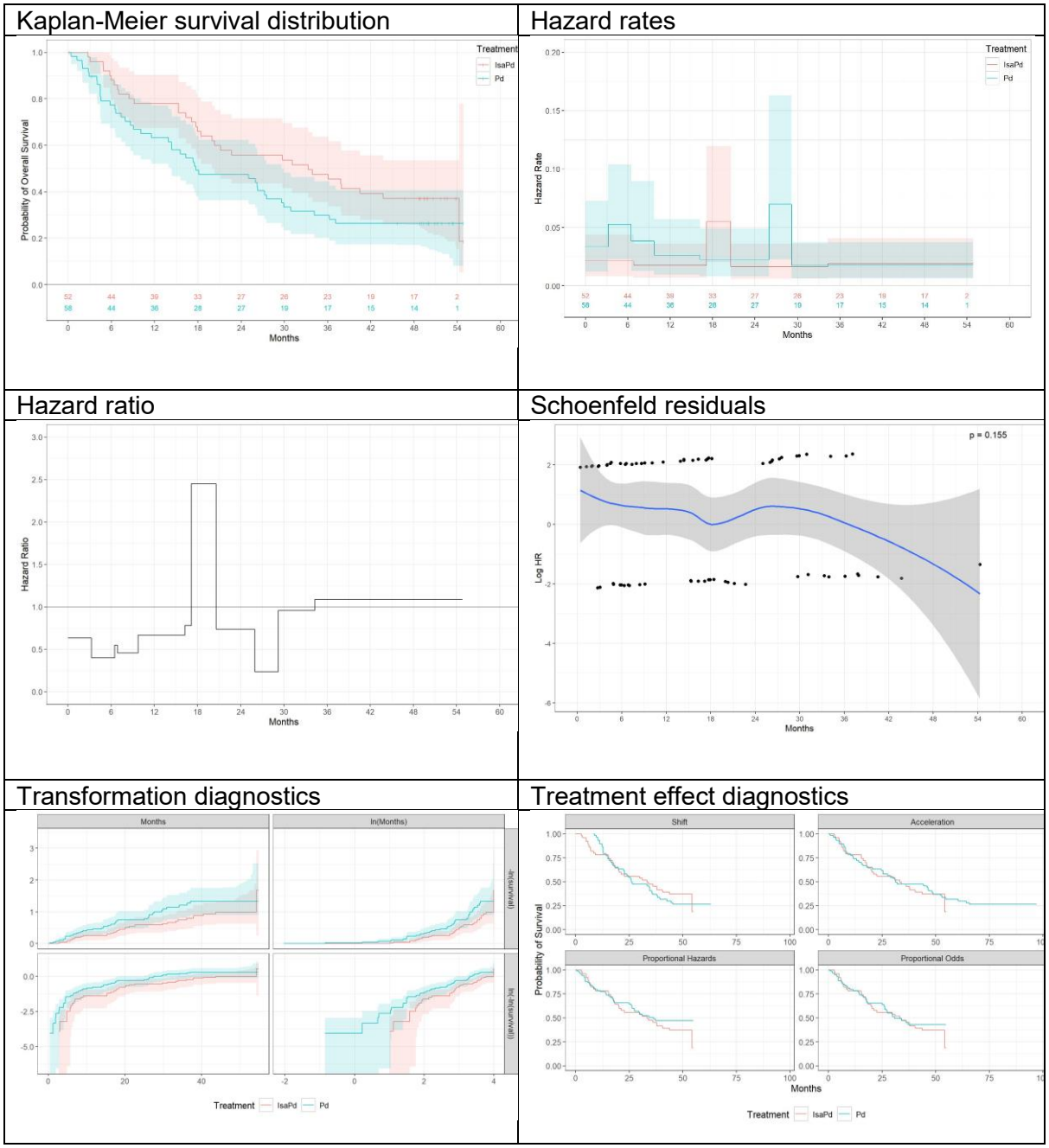


Cut-off date: 27 Jan 2022.
Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; KM, Kaplan-Meier; OS, overall survival; Pd, pomalidomide + dexamethasone.

Diagnostic and PH assumption tests summary

Figure 11 presents the diagnostic information for the OS data from ICARIA-MM for the 4th line population. With the exception of small spikes in months 18–21 for IsaPd and 26–29 for Pd, the smoothed hazards are relatively stable and generally lower for IsaPd up to month 34, after which point they are slightly higher. The test of the linearity of the Schoenfeld residuals was not statistically significant, suggesting that a PH distribution may be appropriate. The slope of the cumulative hazard function for IsaPd is generally diminishing (with a near zero slope at the tail when relatively few patients remain at risk), suggesting a declining hazard over time. The treatment effect diagnostics indicate proportional odds and AFT models may all be appropriate.

Figure 11. OS for the 4th line population of ICARIA-MM, by randomised treatment



Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; OS, overall survival.

Statistical goodness of fit

Goodness of fit was assessed using the BIC and visual inspection of parametric distributions vs KM data from ICARIA-MM. The top six curves with the best statistical fit to the trial (Appendix R) were:

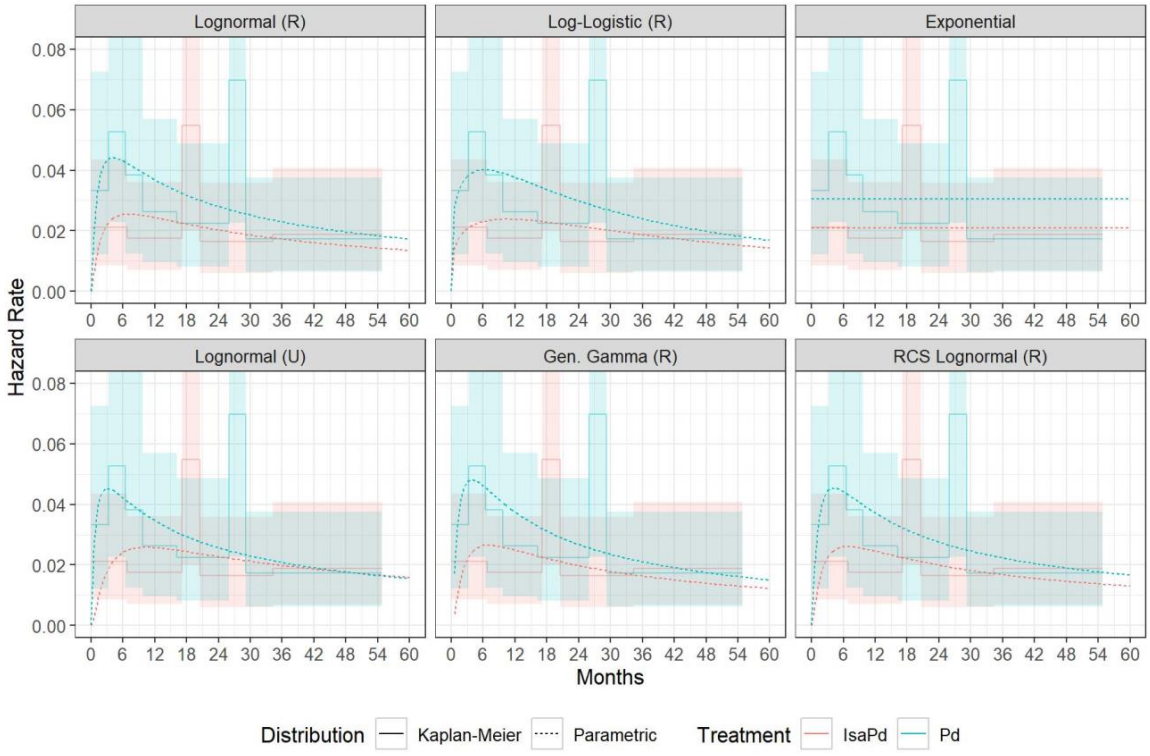
- Log-normal (R)
- Log-logistic (R)

- Exponential
- Log-normal (U)
- Generalised gamma (R)
- RCS log-normal (R).

Hazard rates

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 12. Most of the top six best fitting distributions yield hazard rates which increase initially and then decrease over time except for the exponential which has constant hazards. For all top six distributions, the hazard for IsaPd is projected to be lower than that for Pd throughout the trial follow-up.

Figure 12. Hazard rates for parametric survival distributions fit to OS for the 4th line population from ICARIA-MM, by randomised treatment

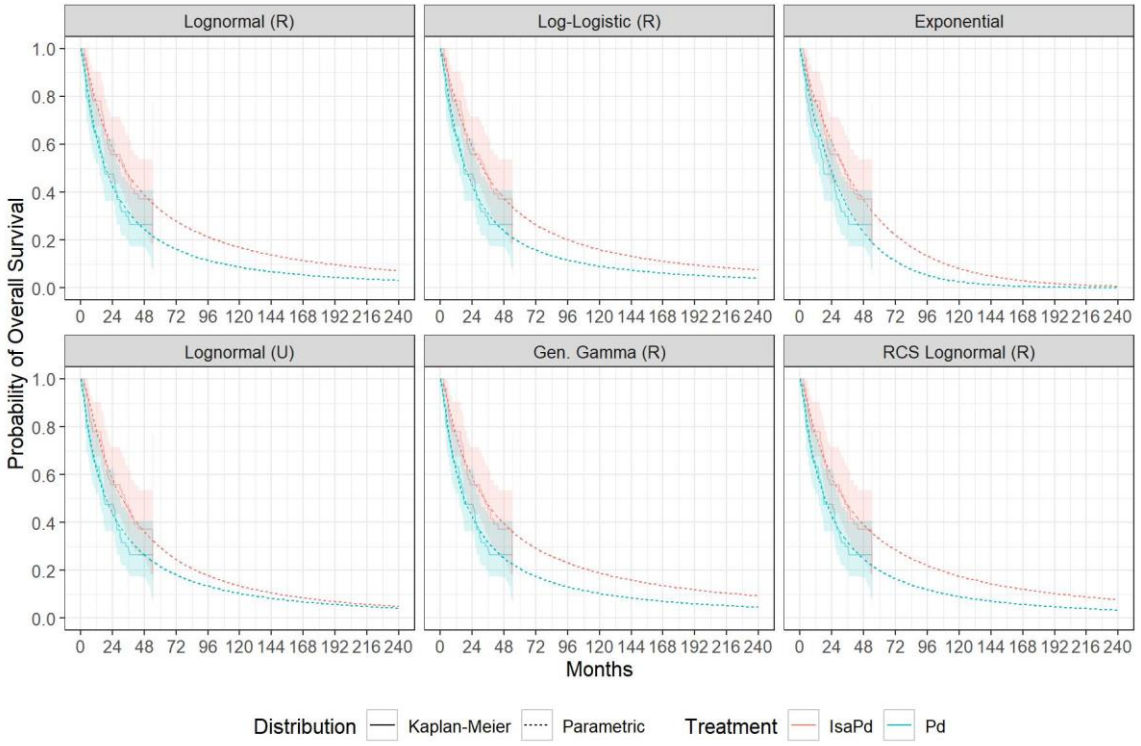


Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; Pd, pomalidomide + dexamethasone; R, restricted; RCS, restricted cubic spline; U, unrestricted.

Goodness of fit – visual inspection

Long-term OS projections (20-year horizon) for the six best statistically fitting curves plotted against OS KM are presented in Figure 13. The restricted log-normal distribution shows long-term separation between the IsaPd and Pd arms, with approximately 10% of the patients in the IsaPd arm and less than 5% in the Pd arm remaining alive at about 14 years. The restricted log-logistic, restricted generalised gamma, and restricted RCS log-normal distributions all have similar shapes and long-term projections, with approximately 10% of Pd patients alive at 10 years and 5% at 14 years. The exponential and unrestricted log-normal have less separation than exhibited for the other curves.

Figure 13. Long-term projections of OS based on parametric survival distributions fit to OS for the 4th line population in ICARIA-MM, by randomised treatment†



†General population mortality not applied.
Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; Pd, pomalidomide + dexamethasone; R, restricted; U, unrestricted.

Selected OS distribution

With longer term follow-up from the ICARIA-MM trial (52.4 months median follow-up), the data is more mature than was available during the initial TA658 appraisal. At the cut-off date (27th January 2022), there were 38.5% of patients in the IsaPd arm and 27.6% of patients in the Pd arm in 4th line population that remained censored for an OS event, limiting the

number of patients informing the tail of the KM. Available evidence from the Pd registration trial (MM-003) which supported the NICE recommendation for Pd [TA427] provided a median OS (13.1 months) that was lower than that seen in the ICARIA-MM trial Pd arm (17.71 months). This data from ICARIA-MM continues to suggest that patients receiving Pd in the trial may have slightly improved outcomes compared with MM-003. Furthermore, RWE studies reporting OS in Pd patients with 3 prior therapies reported median OS of 10.9 months and 9.7 months, suggesting that the survival of Pd patients in real world practice is lower than seen in the trial.

The restricted log-normal distribution was selected in the base case to model IsaPd and Pd OS given that this distribution has a good statistical and visual fit to the trial data for both arms. Approximately 20% of Pd patients survive to five years, 9% to ten years, and 5% to 15 years, which are not unreasonable given the relatively poor prognosis and average age of these patients. Clinical opinion of four highly experienced UK haematologists suggested that the jointly fitted exponential distribution was likely to better represent expected long-term survival in patients receiving treatment at 4th line in UK clinical practice (3). An exponential distribution implies a constant hazard, which is not supported by the trial data from ICARIA-MM. The hazard rate observed in the trial period showed an initial increase and then declines over time, because patients with aggressive disease or those who do not respond to treatment tend to progress quickly compared with those who respond to treatment. Although this distribution was tested in a scenario analyses, it should be noted that IsaPd availability in the UK is recent (~3 years) and therefore choice for long term outcomes are more likely to be anchored on real-world experience with Pd as a reference treatment. The exponential distribution may therefore be more suitable for the extrapolation of Pd OS. An independent fitted log normal distribution for IsaPd (same distribution type as the base case) and independent exponential for Pd have been tested as a scenario analysis (independent model fits presented in Appendix S).

Adjustment for non-UK subsequent therapies

Scenario analyses are presented that adjust the ICARIA-MM OS data to account for the subsequent therapies that would not be received by patients at 5th line+ in NHS clinical practice, as discussed in section B.2.6.1.2.1. , using methods outlined in NICE DSU TSD 16. Estimated OS were adjusted for patients receiving daratumumab after progression on both treatment arms. A list of subsequent therapies received in ICARIA-MM are presented in Table 47. Stratified unadjusted and adjusted HR of IsaPd vs Pd using the IPCW, and simple TSE methods are presented in Table 32.

Table 32. Subsequent therapy adjustment HRs – IsaPd vs Pd

Analysis	HR IsaPd vs Pd (95% CI)
4th line OS HR†	0.657 (0.409, 1.055)
IPCW – daratumumab†	0.650 (0.373 - 1.132)
Simple TSE adjustment†‡	0.618 (0.376, 1.013)

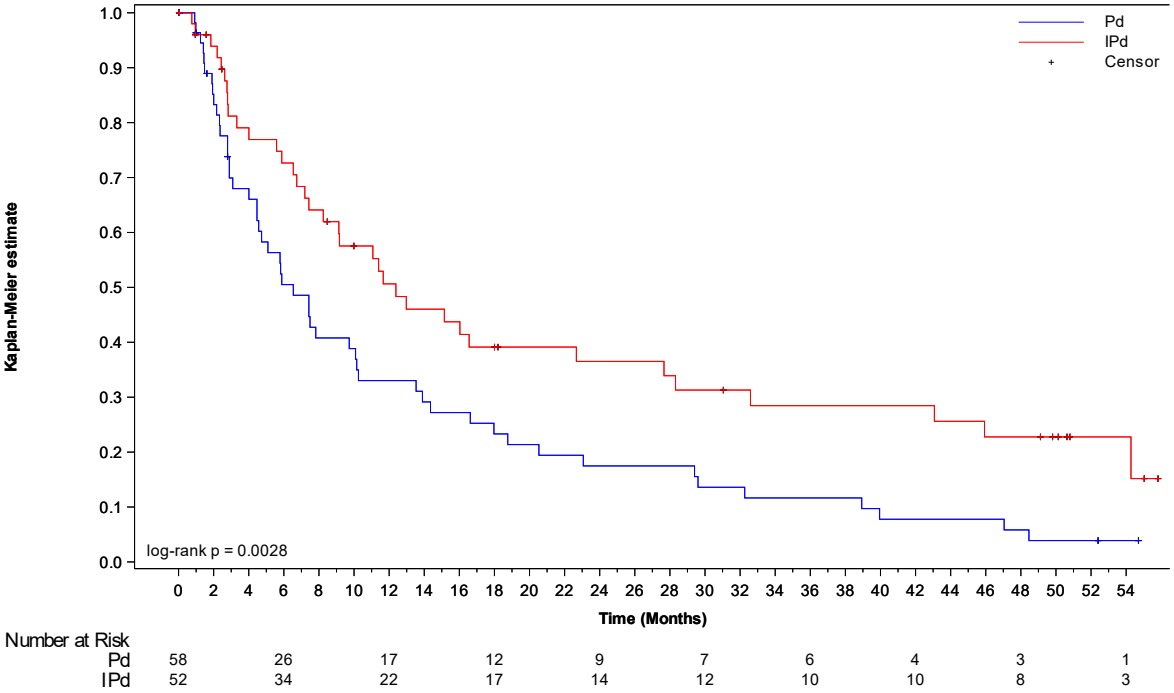
† Stratified on age (<75 years vs >=75 years) according to IRT.
‡Assuming normal distribution of ln (HR) with standard error based on standard deviation of bootstrap estimates
Abbreviations: CI, confidence interval; HR, hazard ratio; IPCW, inverse probability of censoring weighting; IRT, interactive response technology; IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; RPSFT, rank-preserving structural failure time; TSE, two-stage adjustment.

The HR derived from the 4th line subgroup for OS and adjusted HRs are consistent between analyses, suggesting that the effect of subsequent therapies in this patient population is minimal. Both the simple TSE and IPCW adjustment resulted in improved HR estimates of IsaPd vs Pd compared with the base case, suggesting that the unadjusted 4th line HR may be a conservative estimate of comparative efficacy. Therefore, conservatively, no adjustment was made for treatment effectiveness estimate for OS in the model base case. The adjusted HRs have been tested in scenario analyses.

B.3.3.2.1.2. Progression-free survival

IsaPd showed a statistically significant benefit in PFS (investigator assessed) when compared with Pd in the 4th line subgroup with longer follow-up from the ICARIA-MM trial. Median PFS remained significantly longer in the IsaPd arm (12.39 months, 95% CI: 7.43, 27.66) than in the Pd arm (6.54 months, 95% CI: 4.47, 10.09), respectively. The stratified HR was 0.54 (95% CI: 0.34, 0.84). PFS KM data for IsaPd and Pd are presented in Figure 14.

Figure 14. PFS (investigator assessed) KM, 4th line

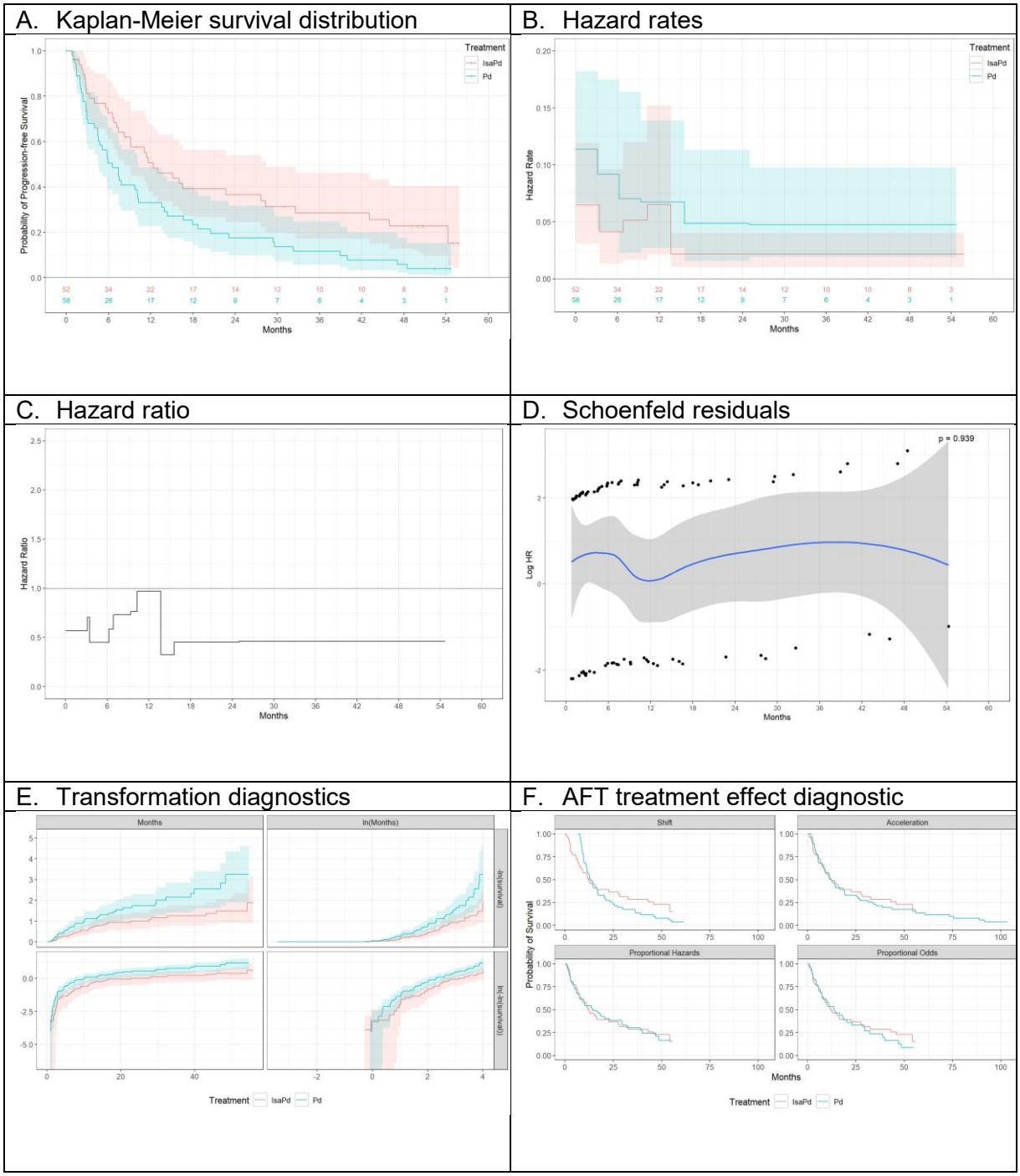


Cut-off date: 14th March 2022
Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; KM, Kaplan-Meier; Pd, pomalidomide + dexamethasone; PFS, progression-free survival.

Diagnostic and PH assumption tests summary

Figure 15 presents the diagnostic information for the PFS data from ICARIA-MM. The hazard rates for the Pd group are decreasing until Month 16, upon which they become more stable. The hazard rates for IsaPd oscillate up and down between Months 3 and 12, after which appear more stable; and are also lower than the hazards for Pd throughout the follow-up period. The HR for IsaPd vs Pd is below 1.0 for most of the follow-up period. The test of the linearity of the Schoenfeld residuals was again not statistically significant, suggesting that a PH distribution (e.g. exponential, Weibull, Gompertz) may be appropriate. The cumulative hazard function has a slightly decreasing slope (apart from 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 models may be most appropriate for PFS.

Figure 15. PFS for the 4th line population of ICARIA-MM, by randomised treatment



Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone.

Statistical goodness of fit

Statistical goodness of fit was assessed using the of parametric distributions vs KM data from ICARIA-MM (Appendix R).

The top six curves with the best statistical fit were:

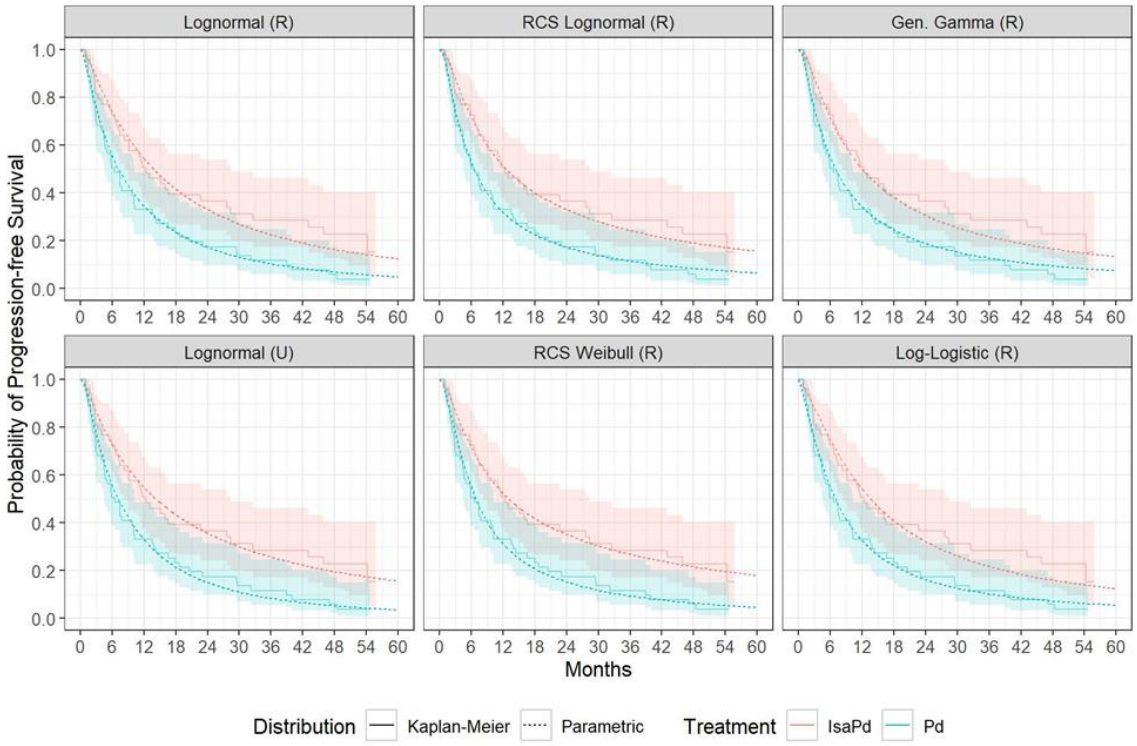
- Log-normal (R)
- RCS Log-normal (R)

- Generalised gamma (R)
- Log-normal (U)
- RCS Weibull (R)
- Log-Logistic (R).

Goodness of fit – visual inspection

To evaluate visual goodness of fit, PFS projections for the six best statistically fitting curves plotted against PFS KM curves are presented in Figure 16.. The distribution with the best visual fit to both arms is the restricted RCS Weibull. The six top fitting distributions generate projections of PFS at 60 months for Pd ranging from approximately 2–8% and for IsaPd ranging from 12–19%.

Figure 16. Parametric survival distributions fit to PFS for the 4th line population in ICARIA-MM, by randomised treatment†

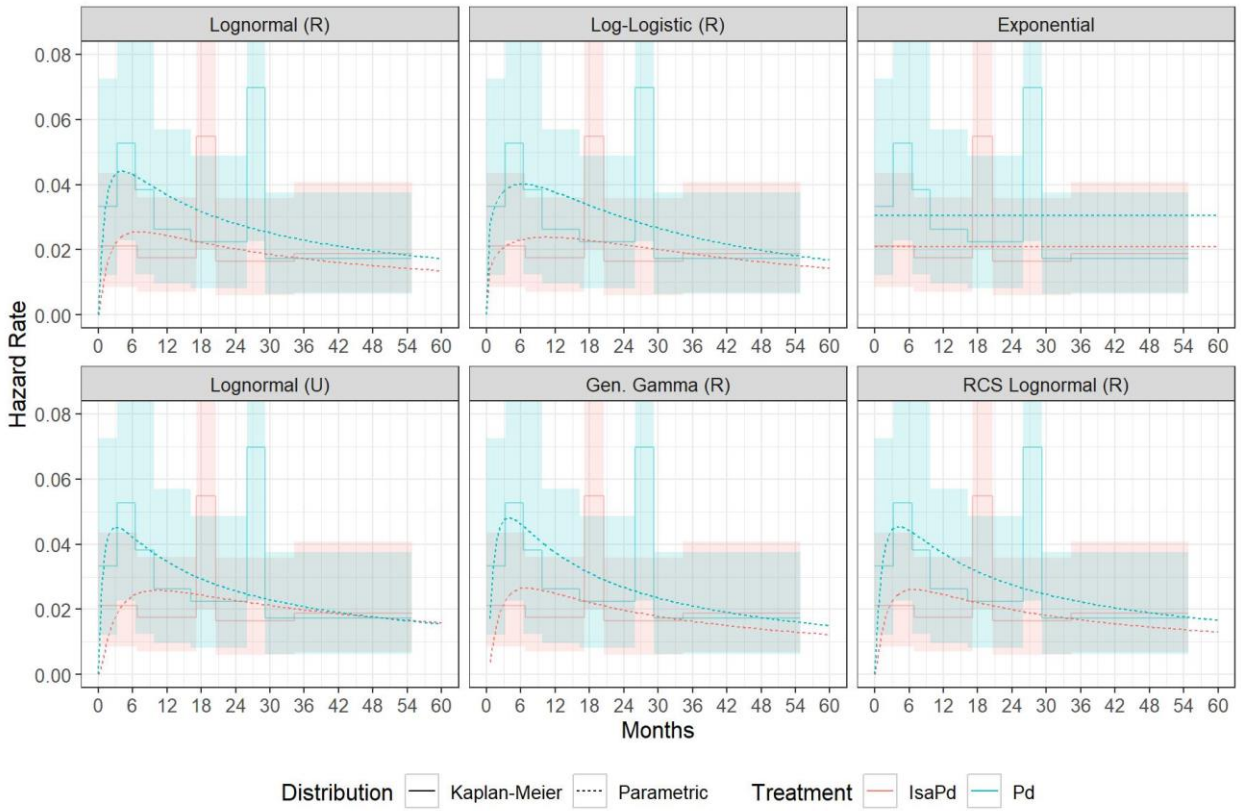


†General population mortality not applied.
Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; PFS, progression-free survival; Pd, pomalidomide + dexamethasone; R, restricted; U, unrestricted.

Hazard rates

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 17. The majority of the top six best fitting distributions yield hazard rates that increase initially and then decrease over time. For all the top six distributions, the hazard for IsaPd is projected to be lower than that for Pd throughout the trial follow-up.

Figure 17. Hazard rates for parametric survival distributions fit to PFS for the 4th line population from ICARIA-MM, by randomised treatment



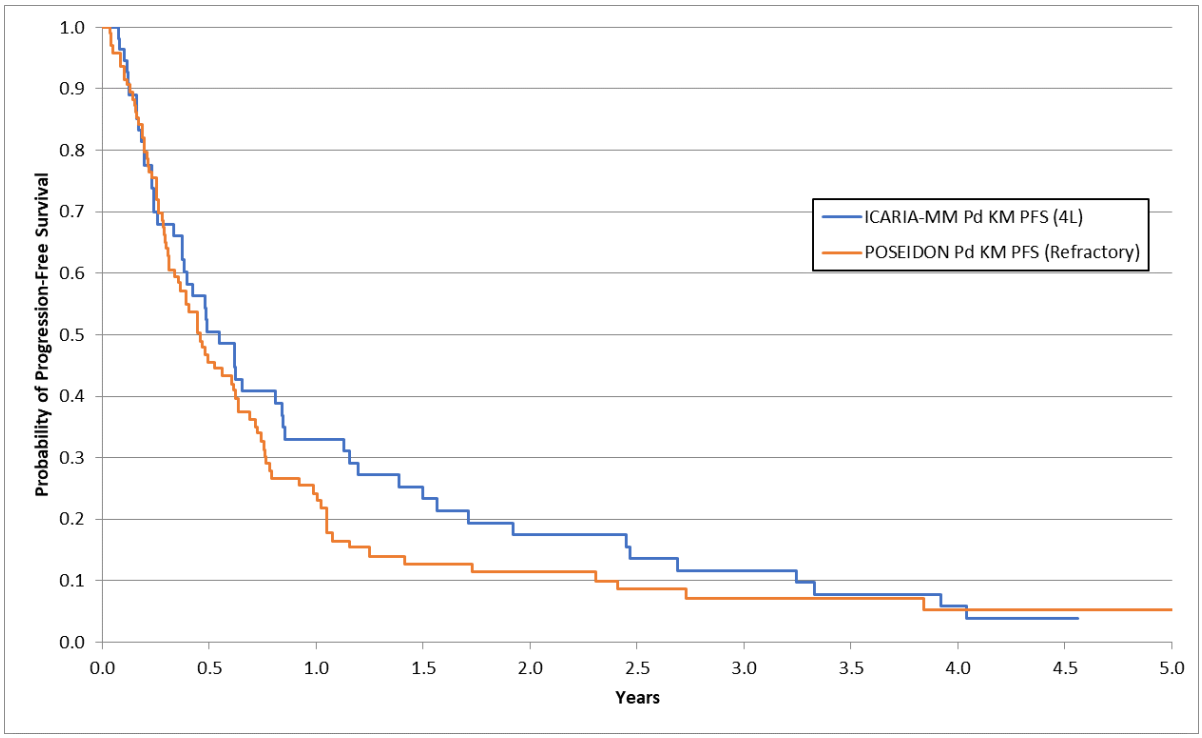
Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; Pd, pomalidomide + dexamethasone; R, restricted; RCS, restricted cubic spline; U, unrestricted.

An RCS Weibull model was used to estimate PFS for IsaPd and Pd in the base case based on statistical goodness of fit (BIC), visual fit, effect diagnostics, and clinical plausibility. PFS estimates for Pd are below 10% at three years, below 5% at five years, and close to zero by 10 years, which are not unreasonable given the poor prognosis of patients reaching 4th line treatment.

There are no external clinical trial data for PFS for patients similar to those in ICARIA-MM receiving IsaPd that could be used to validate long-term PFS predictions. For Pd the non-interventional POSEIDON study, assessing PFS and OS in 3rd line+ RRMM patients treated

with Pd, a more recent study with worldwide study locations including 5 UK locations was used to validate predictions (159). PFS in POSEIDON was generally lower than the Pd arm in ICARIA-MM over a median follow-up time of 43.5 months (maximum follow-up of ~76 months), with estimated PFS at 4 years and 6 years of 5% and 3.5% respectively (Figure 18).

Figure 18. Comparison of 4th line Pd PFS in ICARIA-MM vs Pd PFS in POSEIDON

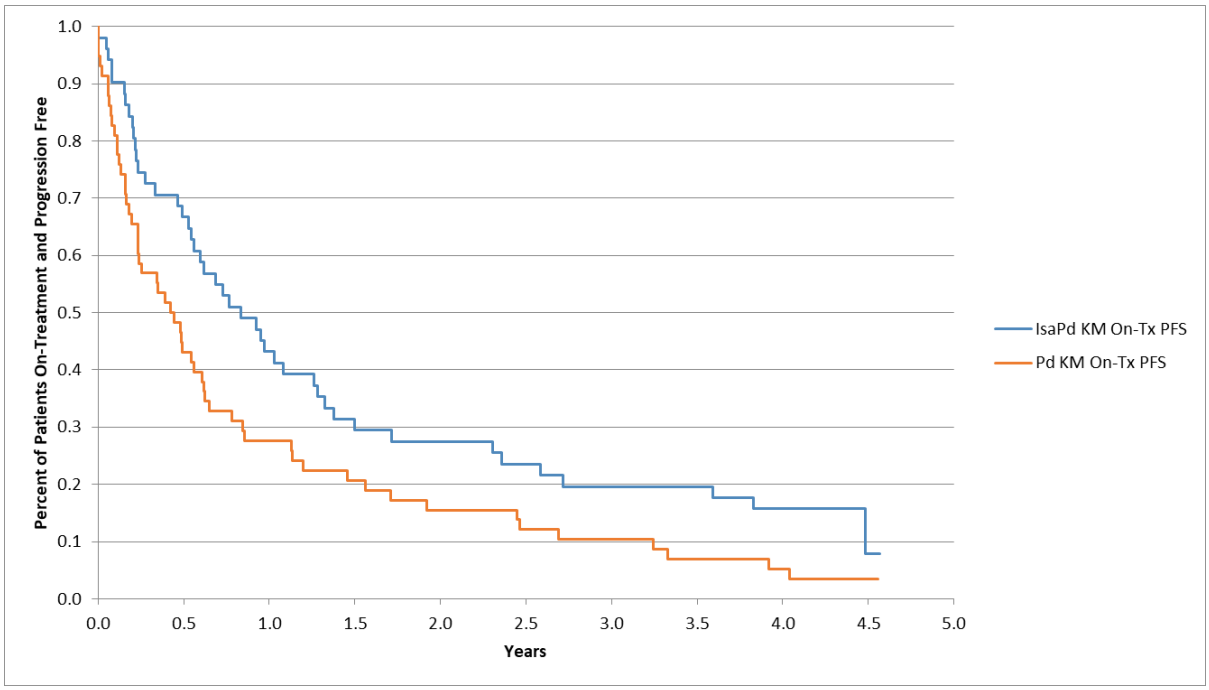


*POSEIDON refractory subgroup population: patients who had progressed on therapy or within 60 days after completing the last prior therapy.
Abbreviations: Pd, pomalidomide + dexamethasone; PFS, progression-free survival.

B.3.3.2.1.3. Progression-free on treatment

The KM data from ICARIA-MM for PFS on treatment are presented in Figure 19.

Figure 19. PFS on treatment KM (4th line subgroup)

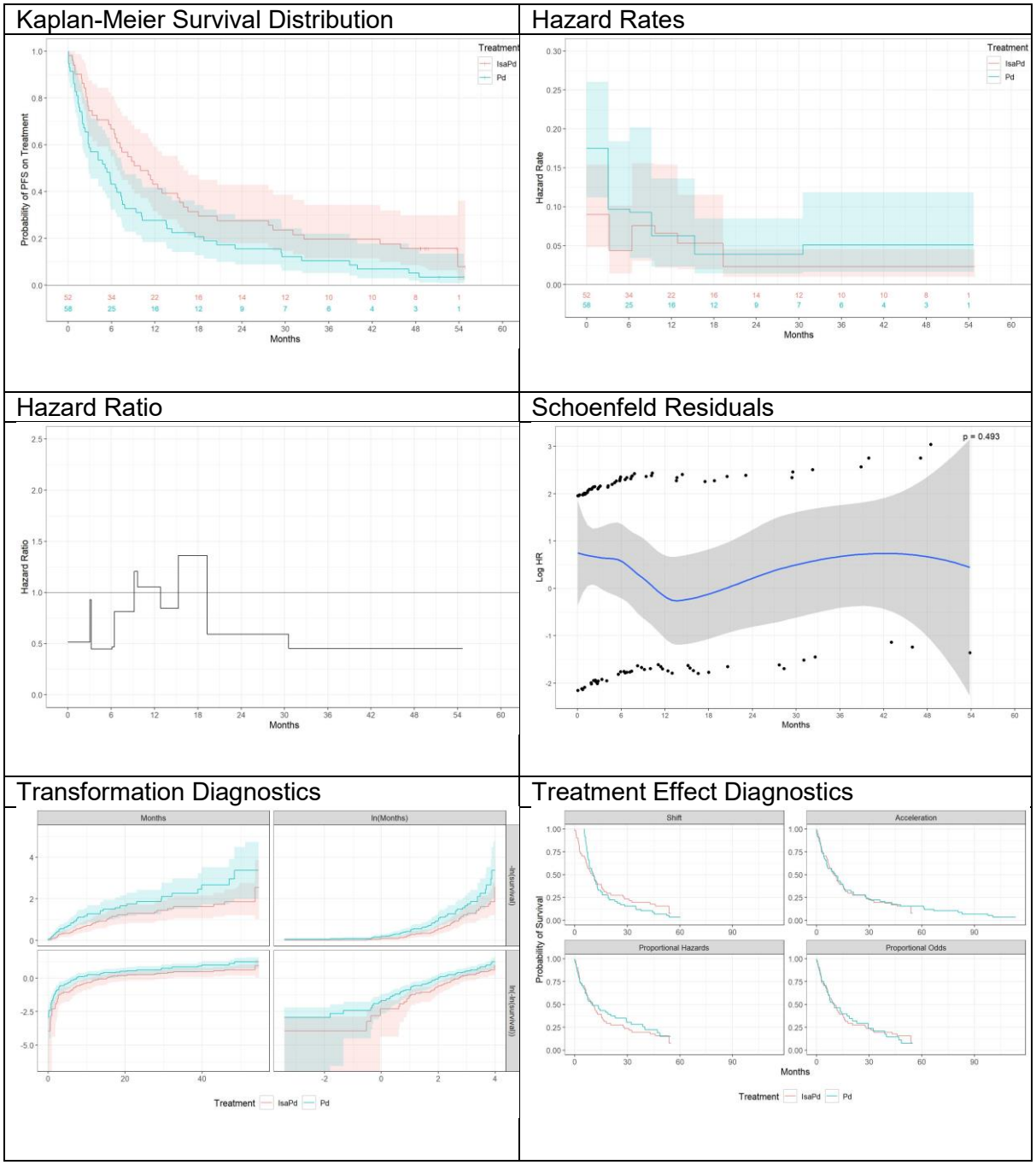


Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; KM, Kaplan-Meier; Pd, pomalidomide + dexamethasone; PFS, progression-free survival.

Diagnostic and PH assumption tests

Figure 20 presents diagnostic information for the PFS on treatment data from ICARIA-MM. Hazard rates for the IsaPd and Pd groups overlap considerably through months 9–18 at which point they stabilise. Rates for IsaPd are generally lower than the hazards for Pd throughout the follow-up period. The HR for IsaPd vs Pd fluctuates throughout the follow-up period and is above 1 for months 9–13 and months 15–20. 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, and that models with proportional odds treatment effects may provide a particularly good fit.

Figure 20. Progression-free survival – on treatment - 4th line population of ICARIA-MM, by randomised treatment



Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone.

Statistical goodness of fit

Goodness of fit was assessed using the BIC (Figure 11) and visual inspection of parametric distributions vs KM data from ICARIA-MM.

The six curves with the best statistical fit were:

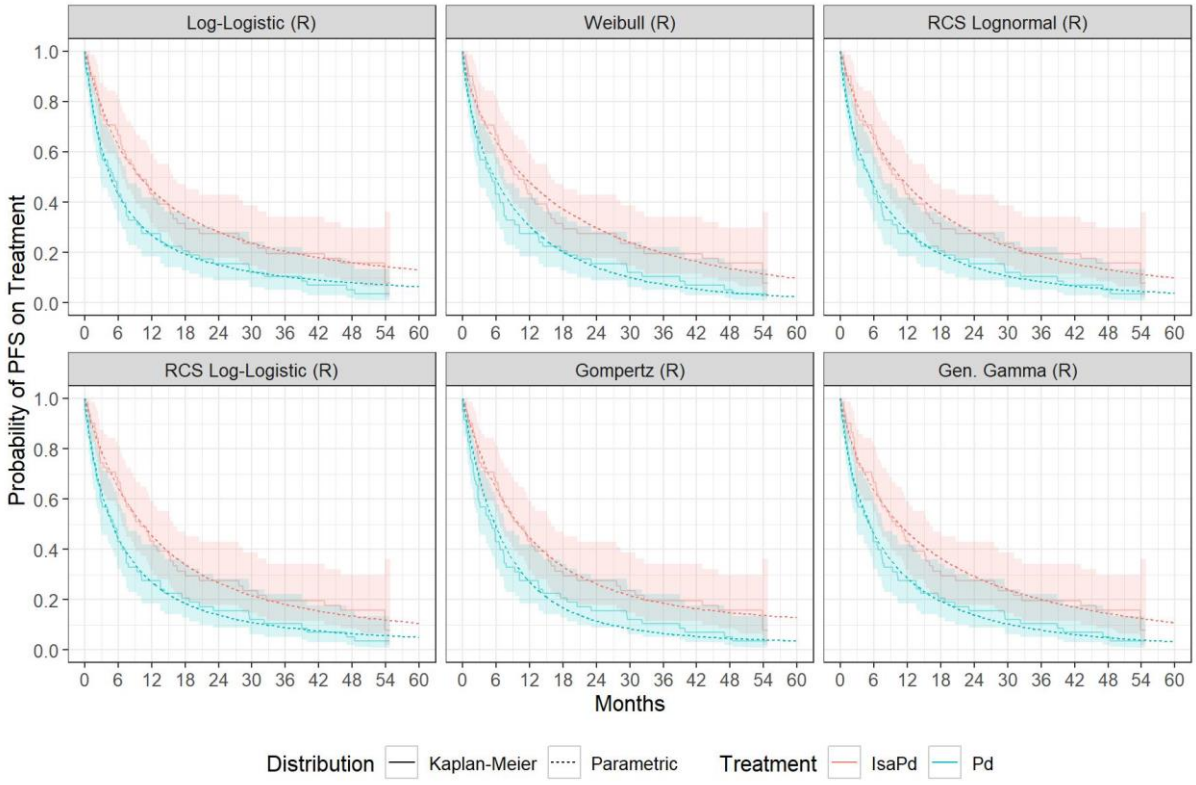
- Log-Logistic (R),

- Weibull (R),
- RCS Log-normal (R),
- RCS Log-Logistic (R),
- Gompertz (R),
- Generalised gamma (R).

Goodness of fit – visual inspection

To evaluate visual goodness of fit, PFS on treatment projections for the six best statistically fitting curves plotted against PFS on treatment KM curves are presented in Figure 21. All six presented curves have a relatively good visual fit to the observed data.

Figure 21. Parametric survival distributions fit to PFS on treatment for the 4th line population in ICARIA-MM, by randomised treatment



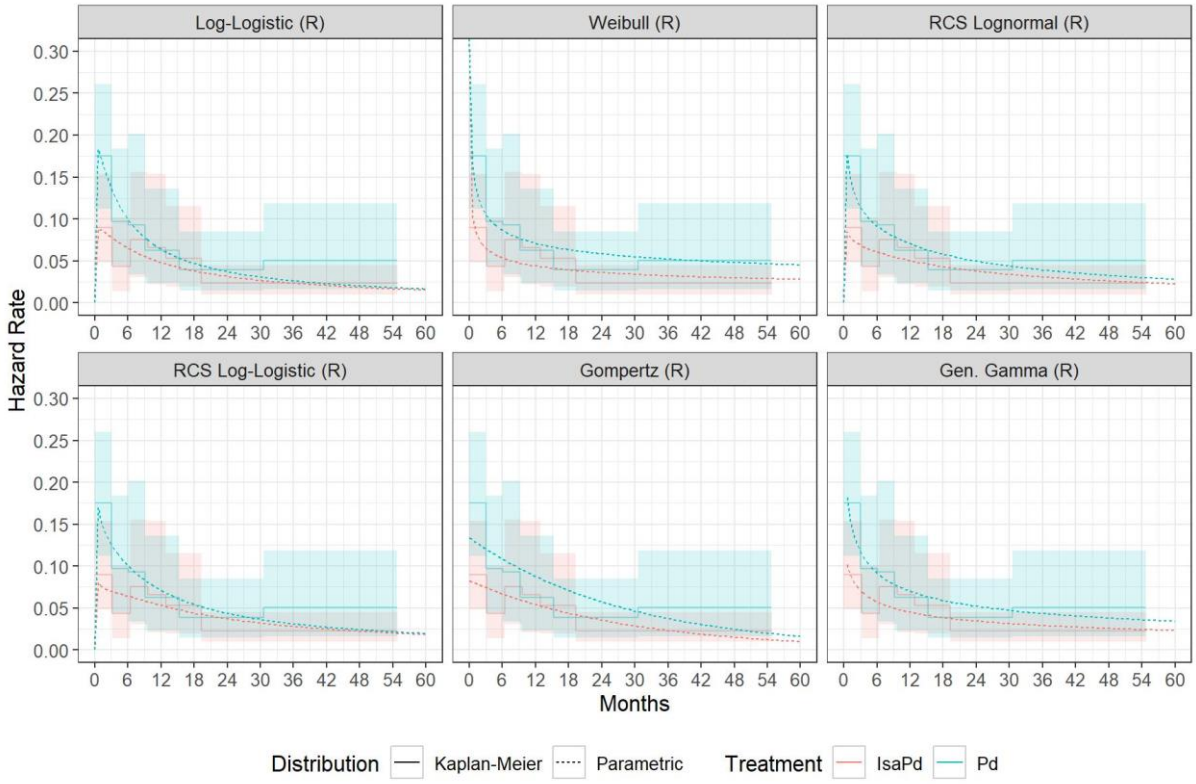
Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; PFS, progression-free survival; Pd, pomalidomide + dexamethasone; R, restricted; RCS, restricted cubic spline; U, unrestricted.

Hazard rates

Hazard rates during the trial follow-up for PFS on treatment for the six best statistically fitting parametric survival distributions were compared with non-parametric hazards (Figure 22). Three of the six distributions yield hazard rates which increase initially and then decrease

over time, consistent with the empirical hazards. For all six distributions, the hazard for IsaPd is estimated to be lower than that for Pd throughout the trial follow-up.

Figure 22. Hazard rates for parametric survival distributions fit to PFS for the 4th line population from ICARIA-MM, by randomised treatment

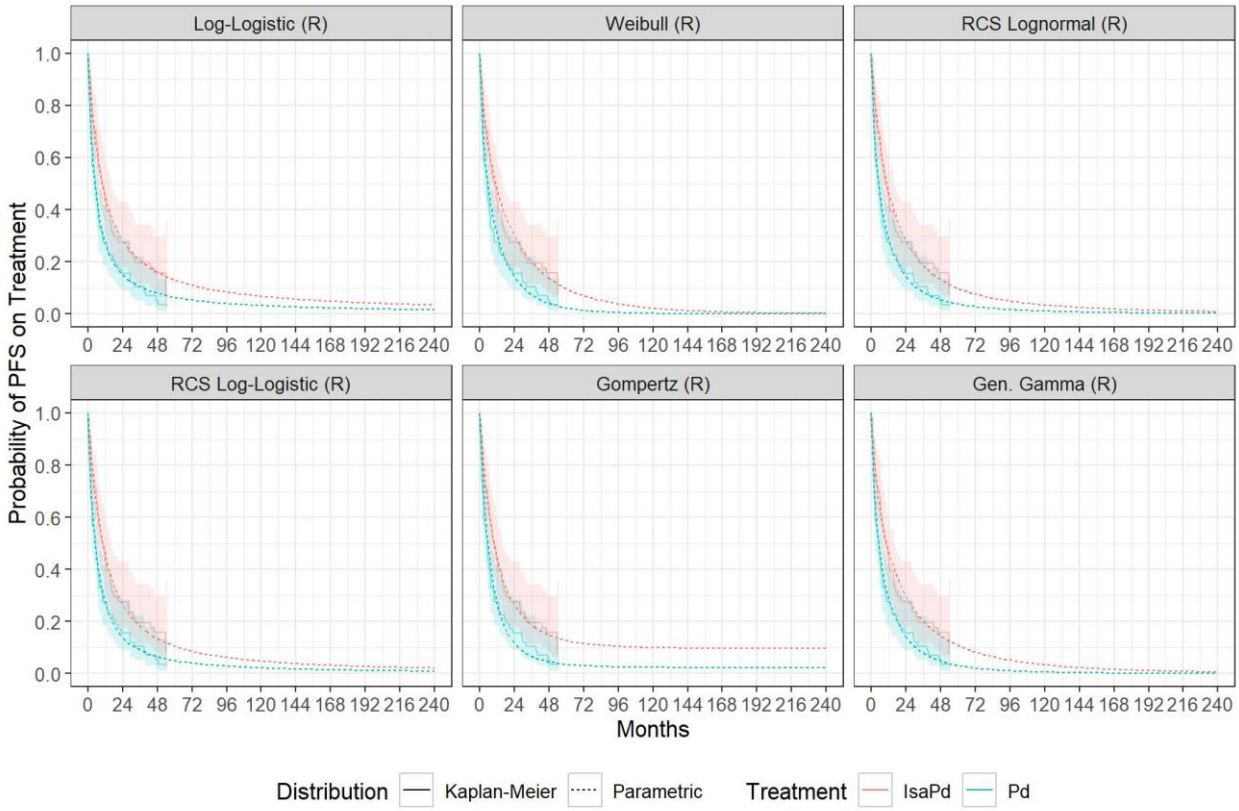


Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; Pd, pomalidomide + dexamethasone; R, restricted; RCS, restricted cubic spline; U, unrestricted.

Long-term projections

Long-term projections of PFS on treatment over a 20-year horizon for the six best statistically fitting curves are presented in Figure 23. All six distributions estimate PFS on treatment to be less than 10% after 10 years. Distributions are relatively similar with the exception of the restricted Gompertz distribution, which functions as a cure model, resulting in a higher PFS on treatment proportion over time.

Figure 23. Long-term projections of PFS-on treatment based on parametric survival distributions fit to PFS for the 4th line population in ICARIA-MM, by randomised treatment



Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; PFS, progression-free survival; R, restricted; RCS, restricted cubic splines; U, unrestricted.

The restricted log-logistic curve was used to estimate PFS on treatment in the base case for IsaPd and Pd. Although there are no external data to validate the estimates, the restricted log-logistic curve provides good statistical (BIC) and visual fit to the trial data and the estimates are clinically plausible given the curves selected for PFS and TTD.

B.3.3.2.1.4. Time to discontinuation

The 4th line TTD KM data from ICARIA-MM is presented in Figure 24 for IsaPd and Pd.

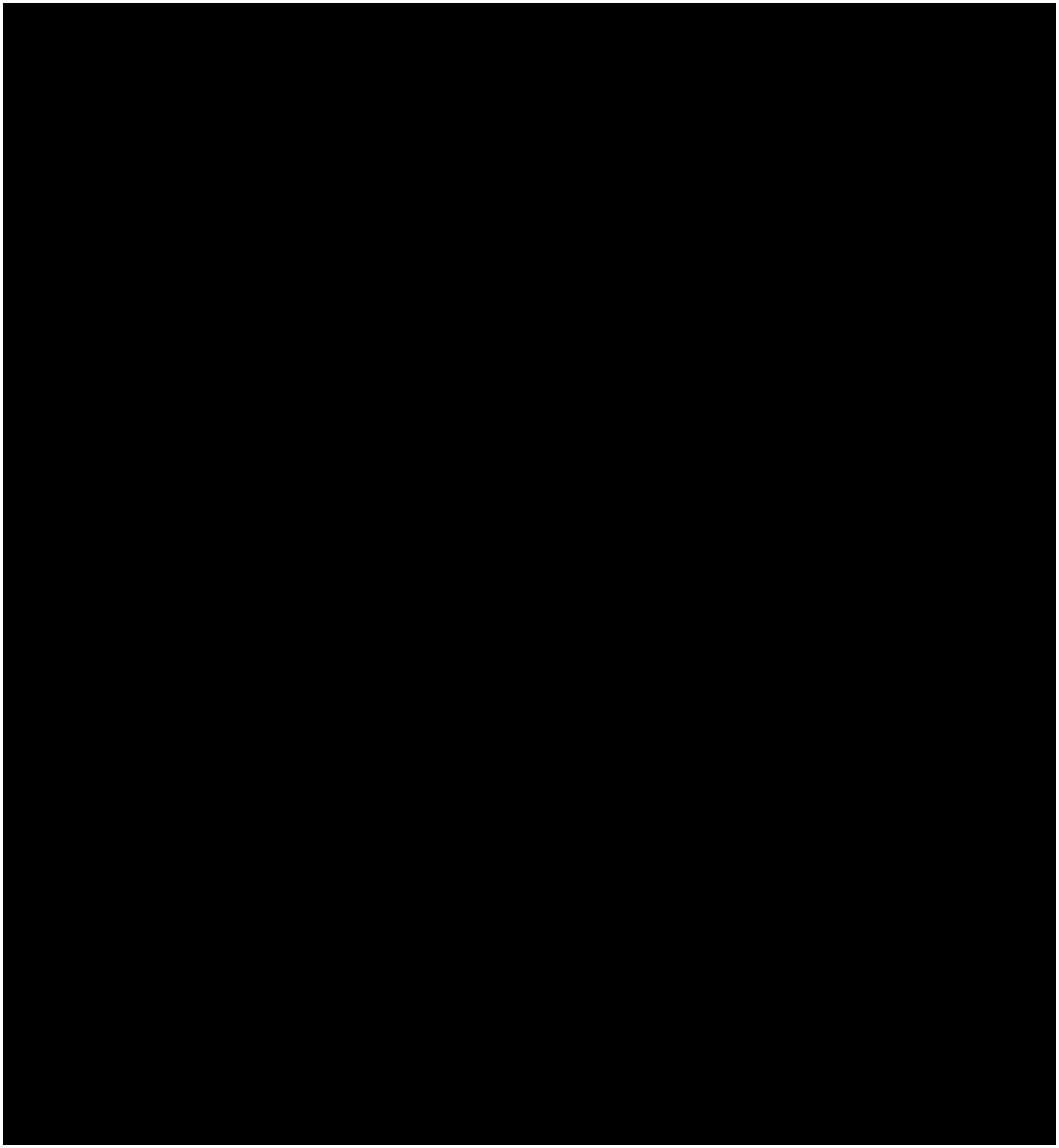
Figure 24. TTD KM (4th line subgroup)

Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; KM, Kaplan-Meier; Pd, pomalidomide + dexamethasone; PFS, progression-free survival; TTD, time to treatment discontinuation.

Diagnostic and PH assumption tests

Figure 25 presents diagnostic information for the TTD data from ICARIA-MM. The smoothed hazard rates for Pd decrease for the first 12 months and then stabilise and are generally higher than IsaPd. The hazard rates for IsaPd are stable for the first 16 months, at which point they decrease and then stabilise again through the remainder of the follow up period. The HR for IsaPd vs Pd generally increases for the first 12 months, at which point it decreases and then stabilises. 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, and that models with proportional odds treatment effects may provide a particularly good fit.

Figure 25. TTD survival for the 4th line population of ICARIA-MM, by randomised treatment



Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; TTD, time to discontinuation.

Statistical goodness of fit

Goodness of fit was assessed using BIC (Appendix R) and visual inspection of parametric distributions vs KM data from ICARIA-MM (Figure 26).

The curves with the best statistical fit were:

- Log-normal (R)

- Log-logistic (R)
- Gompertz (R)
- RCS Log-normal (R)
- Generalised gamma (R)
- Log-normal (U).

Goodness of fit – visual inspection

To evaluate visual goodness of fit, TTD projections for the six best statistically fitting curves plotted against TTD KM curves are presented in Figure 26. The restricted log-normal distribution provides the best visual fit to the KM data.

Figure 26. Parametric survival distributions fit to TTD for the 4th line population in ICARIA-MM, by randomised treatment

Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; R, restricted; TTD, time to discontinuation; U, unrestricted.

Hazard rates

Hazard rates are presented for the six best statistically fitting parametric survival distributions compared with non-parametric hazards are presented in Figure 27. Majority of the presented curves yield hazard rates which initially increase and then decrease over time. However, monotonically decreasing hazards over time are observed for the restricted Gompertz curve.

In all presented distributions, the TTD hazard for IsaPd is estimated to be lower than Pd throughout the trial follow-up.

Figure 27. Hazard Rates for parametric survival distributions fit to TTD for the 4th line population from ICARIA-MM, by randomised treatment

Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; R, restricted; RCS, restricted cubic spline; TTD, time to discontinuation; U, unrestricted.

Long-term projections

Long-term projections of TTD over a 20-year horizon for the six best statistically fitting distributions are presented in Figure 28. All distributions estimate TTD for IsaPd and Pd to be less than 5% by 10 years. The restricted log-normal displays a similar shape to the remaining five curves (apart from the restricted Gompertz, which is essentially a cure model), and has a relatively steep decline and is at or below 10% in both arms by 72 months.

Figure 28. Long-term projections of TTD based on parametric survival distributions fit to TTD for the 4th line population in ICARIA-MM, by randomised treatment

Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; R, restricted; RCS, restricted cubic spline; TTD, time to discontinuation; U, unrestricted.

Selected TTD distribution

The restricted log-normal distribution was used to estimate TTD for IsaPd and Pd in the base case. The restricted log-normal curve provided the best statistical and visual fit to the KM data and provides clinically plausible estimates for patients remaining on treatment, with few patients (<5%) remaining on treatment at 10 years in either arm.

B.3.3.2.2. Comparison vs daratumumab

Due to the limitations of the MAIC discussed in B.2.9 (further details are provided in Appendix P), the SACT data was chosen as it the best available to inform the clinical data for the comparison of IsaPd with daratumumab monotherapy. Although these analyses are inherently limited due to unadjusted differences in baseline characteristics of patients and the lack of individual patient level data available from SACT for matching, SACT datasets provide useful real-world evidence for IsaPd and daratumumab monotherapy in NHS clinical practice, align with the committee's preferred data source for daratumumab in TA783, and more closely aligns to the population relevant to the decision problem (5).

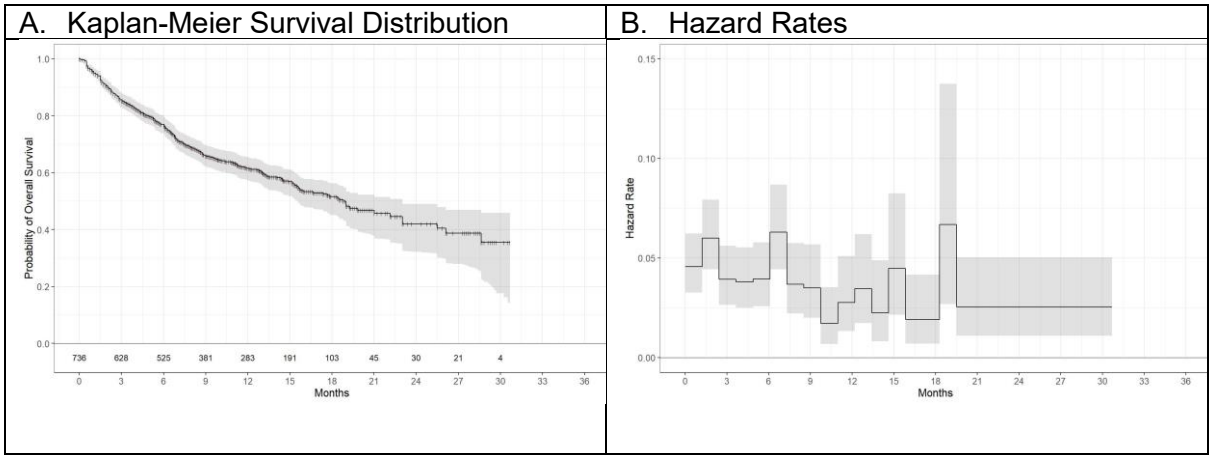
Only OS and treatment duration data are available from the SACT datasets for both IsaPd and daratumumab, therefore it is assumed that patients discontinue treatment upon progression, i.e. the PFS-on treatment curve is equal to the TTD curve, as per the company's analysis in TA783. Curve selection for both treatments followed the same process outlined in Section B.3.3.2.1.

B.3.3.2.2.1. Overall survival

IsaPd SACT

The OS KM and hazard rate for the IsaPd SACT population are reported in Figure 29.

Figure 29. Overall survival – IsaPd SACT population



Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; SACT, systemic anti-cancer therapy.

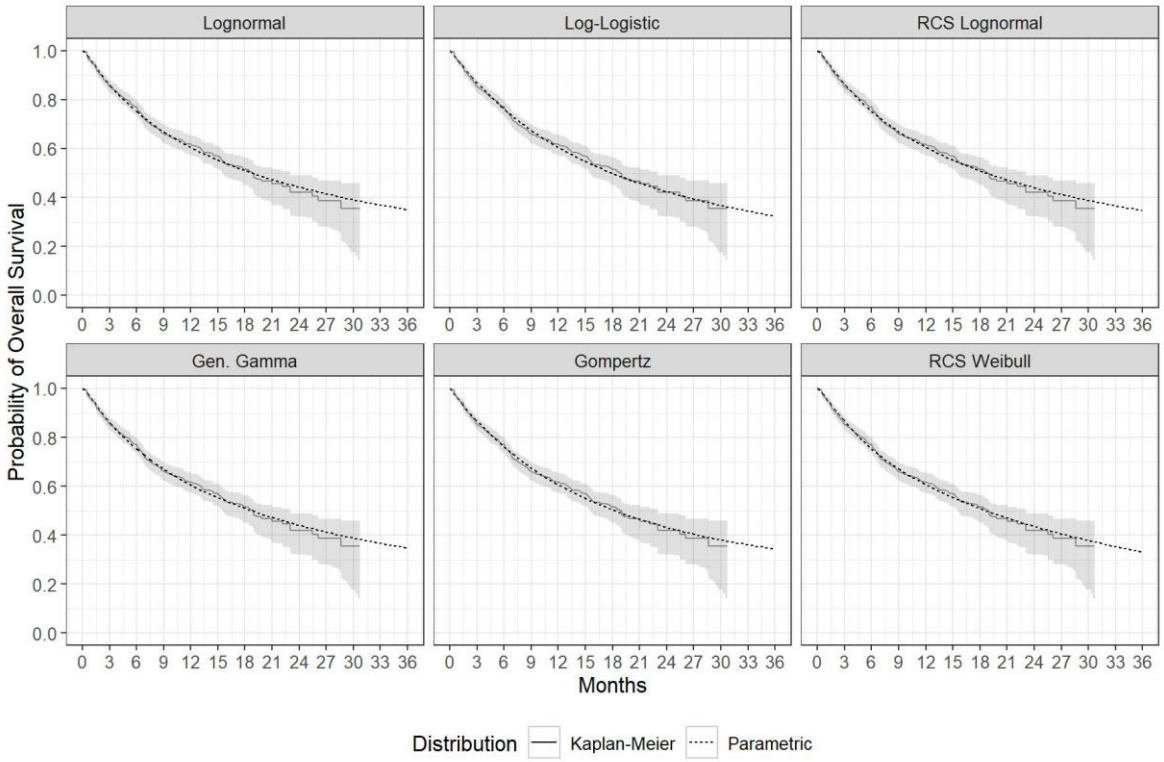
A ranking of parametric distributions fit to OS by the fit statistics are presented in Appendix R. The top six distributions according to BIC statistic were as follows:

- Log-normal
- Log-logistic

- RCS log-normal
- Generalised gamma
- Gompertz
- RCS Weibull.

Parametric survival distributions for OS during the follow up period for the six best fitting distributions based on BIC are shown in Figure 30 (distributions are ranked by BIC going left to right, top to bottom).

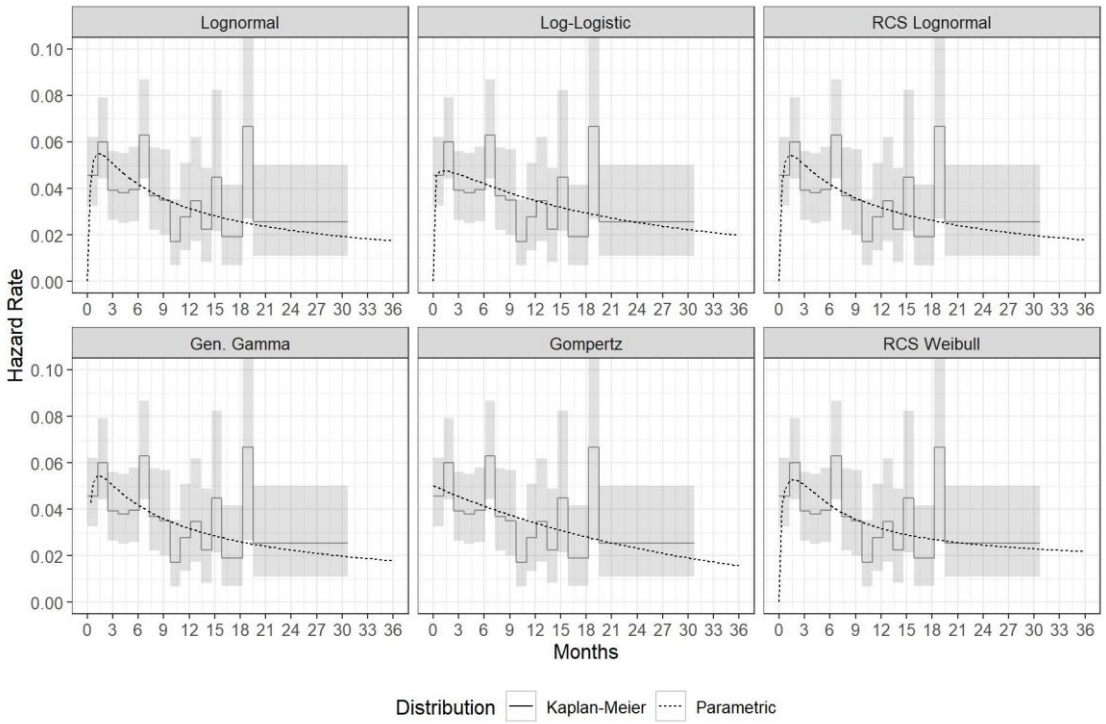
Figure 30. Parametric survival distributions fit to OS – IsaPd SACT population



Abbreviations: Gen. generalised; IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy.

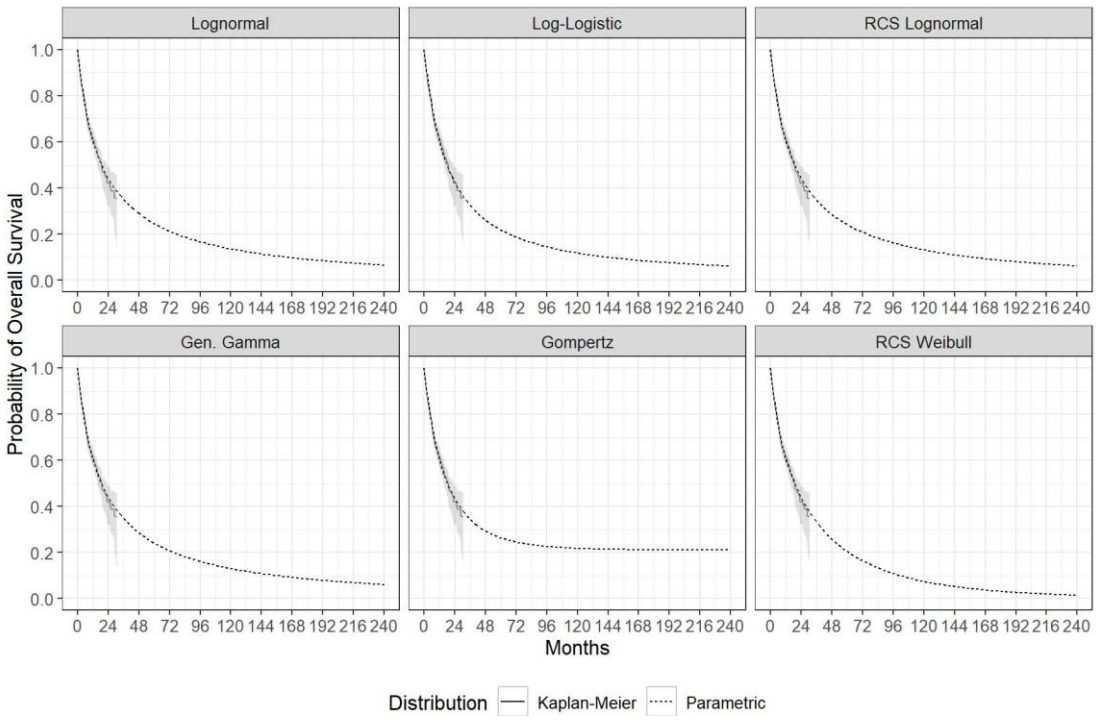
Hazard rates during follow-up for the top six best fitting parametric survival distributions based on BIC for OS are compared with non-parametric hazards in Figure 31. Long-term projections of OS (to 20 years) for these six distributions are shown in Figure 32.

Figure 31. Hazard rates for parametric survival distributions fit to OS – IsaPd SACT population



Abbreviations: Gen. generalised; IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy.

Figure 32. Long-term projections of OS based on parametric survival distributions fit to OS – IsaPd SACT population



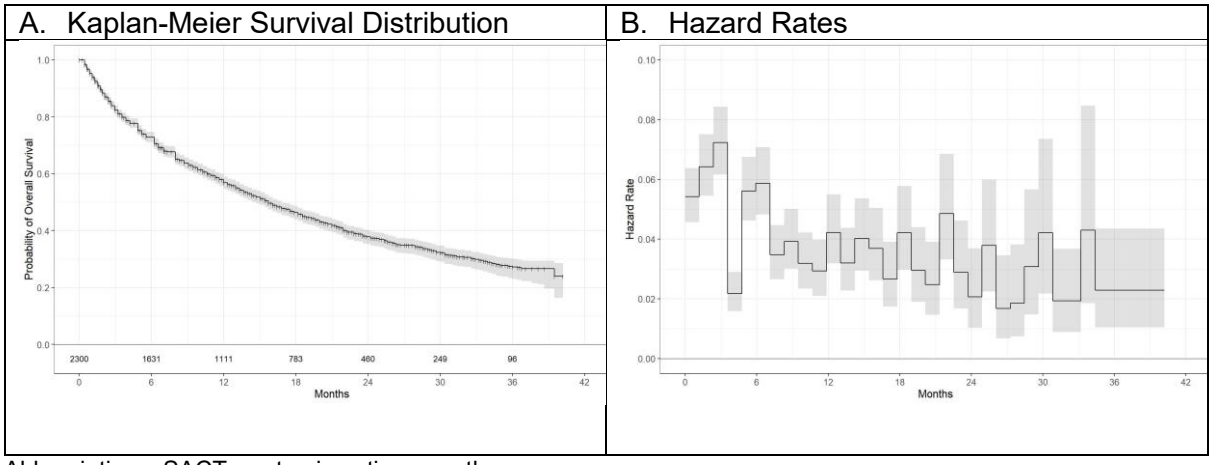
Abbreviations: Gen, generalised; IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy.

The log-normal distribution was used in the base case based on visual and statistical goodness of fit. Also, this distribution yields projections for IsaPd OS that is near the middle of the range of estimates from the various distributions considered, with projection of OS for IsaPd that are approximately 20% at six years, 10% at 14 years, and ~6% at 20 years, which is not unreasonable considering the poor prognosis and age of these patients (median age ~70 years in IsaPd SACT dataset).

Daratumumab SACT

KM survival distribution and hazard rates for OS for the daratumumab SACT population are reported in Figure 33.

Figure 33. Overall survival – daratumumab SACT Population



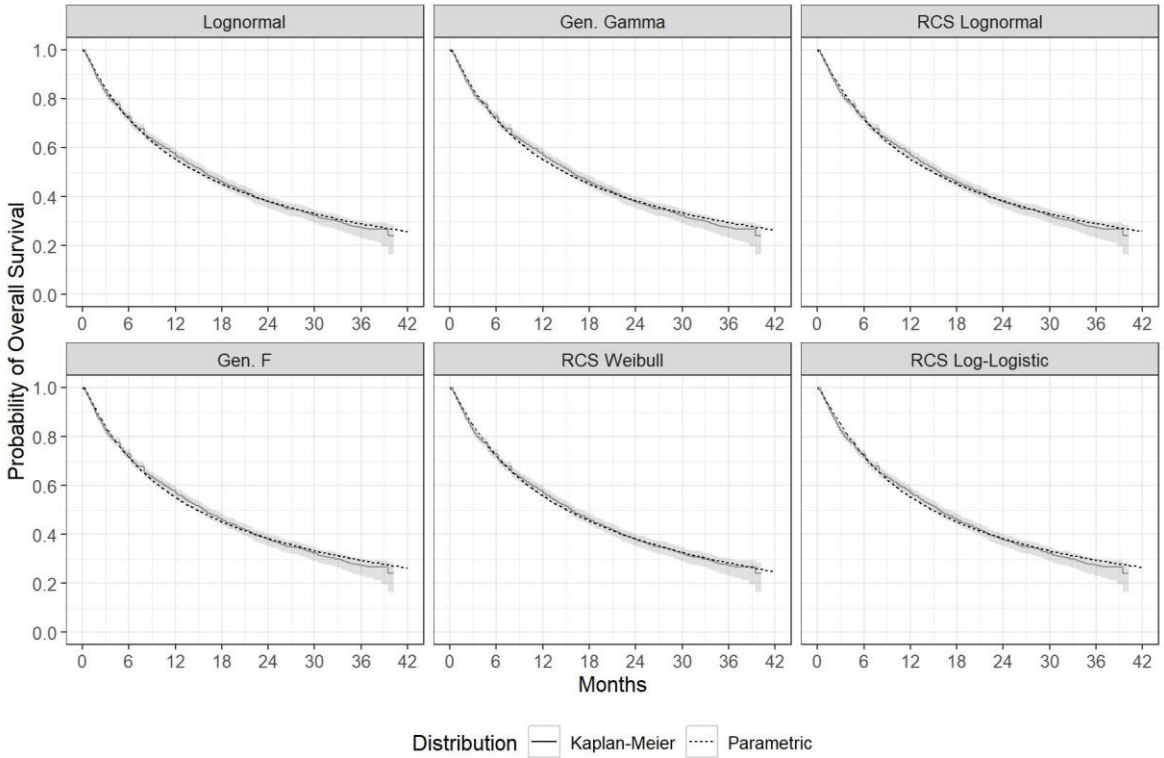
Abbreviations: SACT, systemic anti-cancer therapy.

A ranking of parametric distributions fit to OS by the fit statistics are shown in Figure 34. The top six distributions, according to BIC statistic were as follows:

- Log-normal
- Generalised gamma
- RCS log-normal
- Generalised F
- RCS Weibull
- RCS log logistic.

Parametric survival distributions for OS during the follow up period for the six best fitting distributions based on BIC are shown in Figure 34 (distributions are ranked by BIC going left to right, top to bottom).

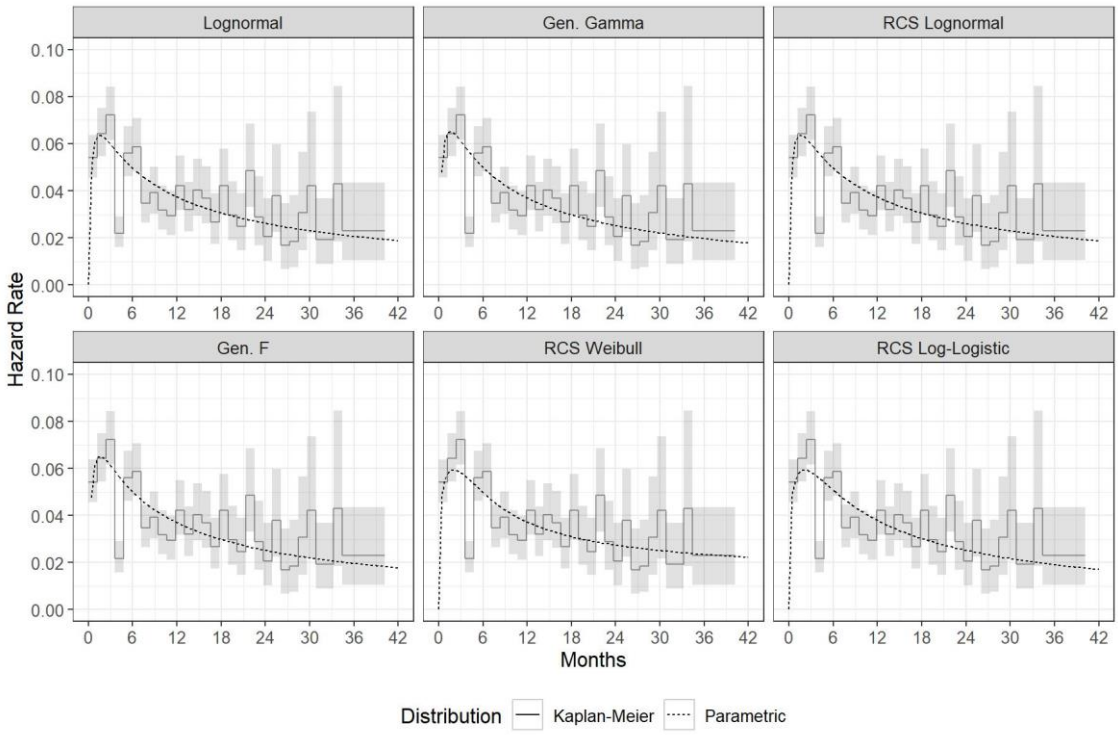
Figure 34. Parametric survival distributions fit to OS – daratumumab SACT population



Abbreviations: Gen. generalised; OS, overall survival; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy.

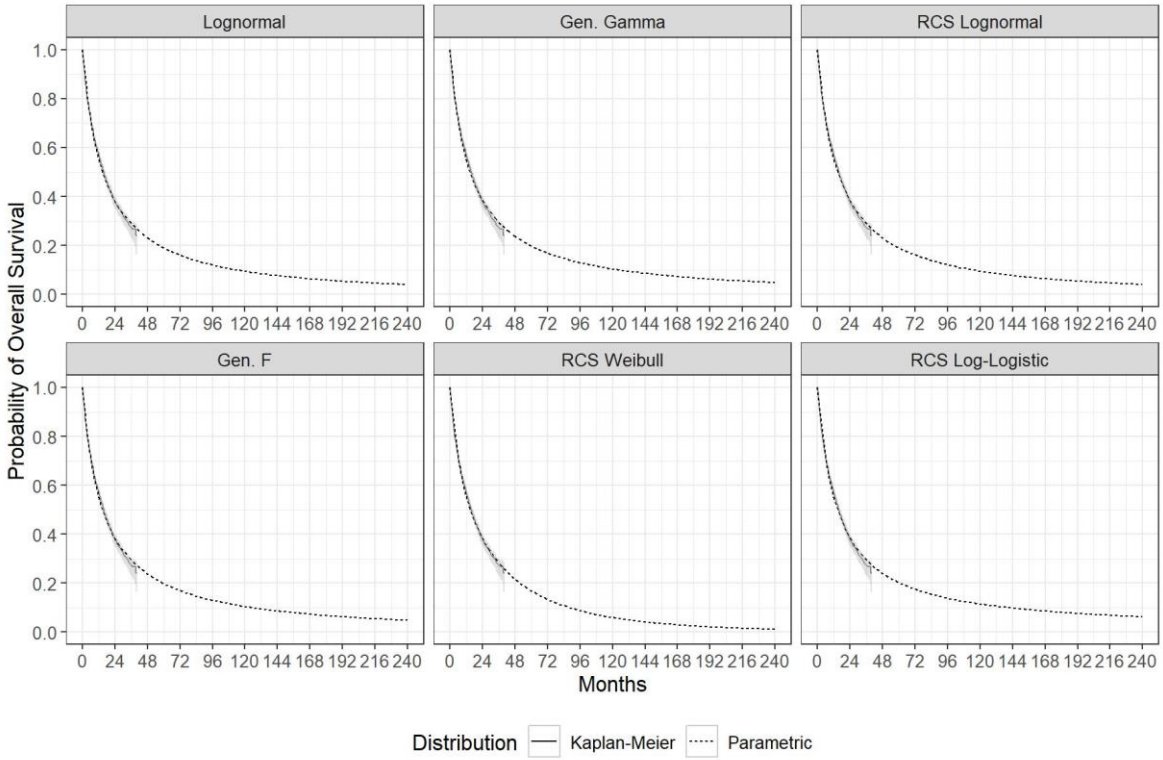
Hazard rates during follow-up for the top six best fitting parametric survival distributions based on BIC for OS are compared with non-parametric hazards in Figure 35. Long-term projections of OS (out to 20 years) for these six distributions are shown in Figure 36.

Figure 35. Hazard rates for parametric survival distributions fit to OS – daratumumab SACT population



Abbreviations: Gen, generalised; OS, overall survival; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy.

Figure 36. Long-term projections of OS – daratumumab SACT population



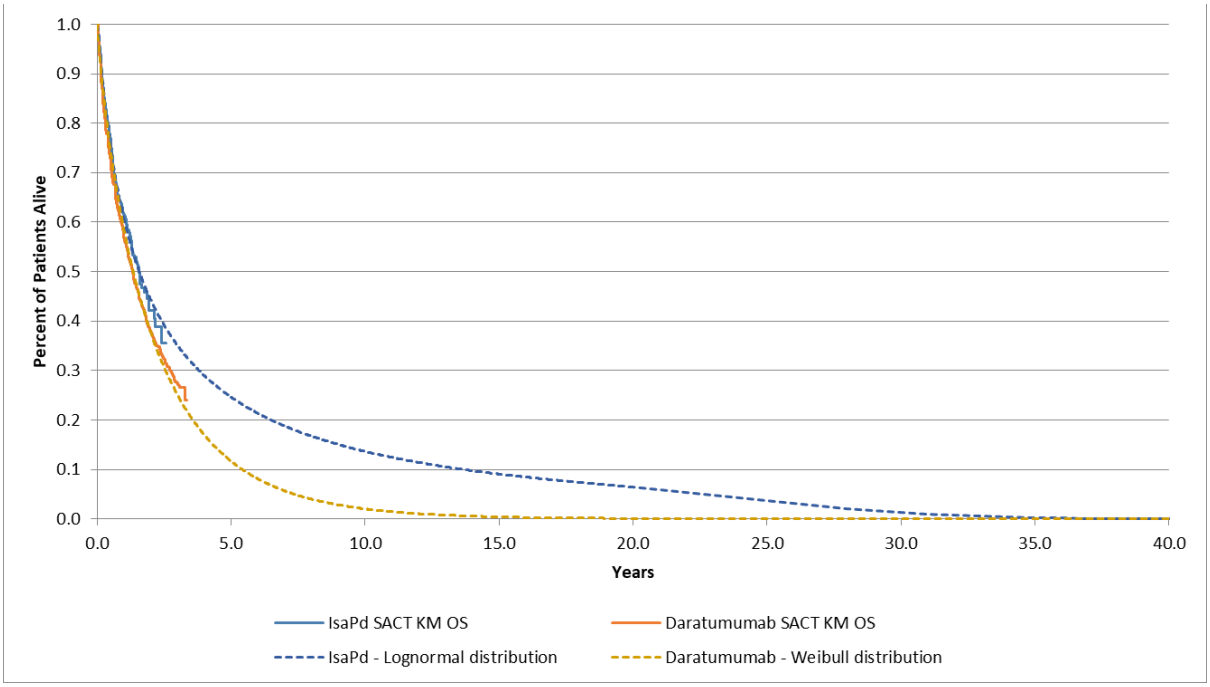
Abbreviations: OS, overall survival; RCS, restricted cubic spline; SACT, systemic anti-cancer therapy.

In TA783, the ERGs preferred distribution to fit to the daratumumab SACT OS data was a Weibull distribution, due to its more conservative estimates of long-term survival (5). Therefore, the Weibull distribution was used in the base case to align with TA783. The Weibull distribution was associated with the 3rd lowest RMST of the presented distributions. The Weibull distribution for daratumumab predicts OS to be approximately 8% at six years, 1% at 14 years, and ~0.01% at 20 years.

IsaPd SACT and daratumumab SACT

The base case OS distributions for IsaPd (Lognormal) and daratumumab (Weibull) and the KM from the respective SACT datasets over the modelled time horizon are presented in Figure 37.

Figure 37. IsaPd and daratumumab SACT OS KM curves and base case distributions



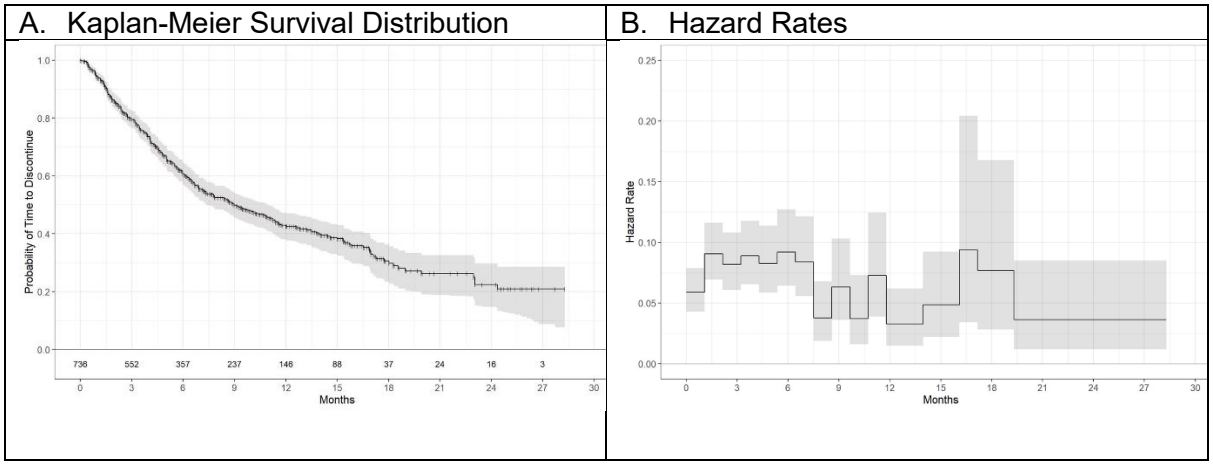
Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; KM, Kaplan-Meier; OS, overall survival; SACT, Systemic Anti-Cancer Therapy dataset.

B.3.3.2.2.2. Treatment duration (TTD)

IsaPd SACT

The treatment duration/TTD KM and hazard rate for the IsaPd SACT population are reported in Figure 38.

Figure 38. TTD – IsaPd SACT population



Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; SACT, systemic anti-cancer therapy; TTD, time-to-treatment discontinuation.

A ranking of parametric distributions fit to TTD by the fit statistics are shown in Appendix R. The top six distributions according to BIC statistic were as follows:

- Log-normal
- Log-logistic
- RCS log-normal
- Generalised gamma
- Gompertz,
- RCS Weibull.

Parametric survival distributions for TTD during the follow up period for the six best fitting distributions based on BIC are shown in Figure 39 (distributions are ranked by BIC going left to right, top to bottom). In visual inspection of the survival distributions, the lognormal has a good fit to the KM curve, although it may provide a slight overestimation when compared with the log-logistic.

Figure 39. Parametric survival distributions fit to TTD – IsaPd SACT population

Abbreviations: Gen., generalised; IsaPd, isatuximab + pomalidomide + dexamethasone; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy; TTD, time-to-treatment discontinuation.

Hazard rates during follow-up for the top six best fitting parametric survival distributions based on BIC for TTD are compared with non-parametric hazards in Figure 40. Long-term projections of TTD out to 20 years for these six distributions are shown in Figure 41. Most of the distributions yield projections of TTD for IsaPd of around 15% by 10 years, apart from the Gompertz and RCS Weibull. The lognormal displays a similar shape to the remaining five curves (with the exception of the Gompertz, which is essentially a cure model), and has a slow decline and is at or below 10% by 14 years.

Figure 40. Hazard rates for parametric survival distributions fit to TTD – IsaPd SACT population

Abbreviations: Gen. generalised; IsaPd, isatuximab + pomalidomide + dexamethasone; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy; TTD, time-to-treatment discontinuation.

Figure 41. Long-term projections of TTD based on parametric survival distributions fit to TTD – IsaPd SACT population

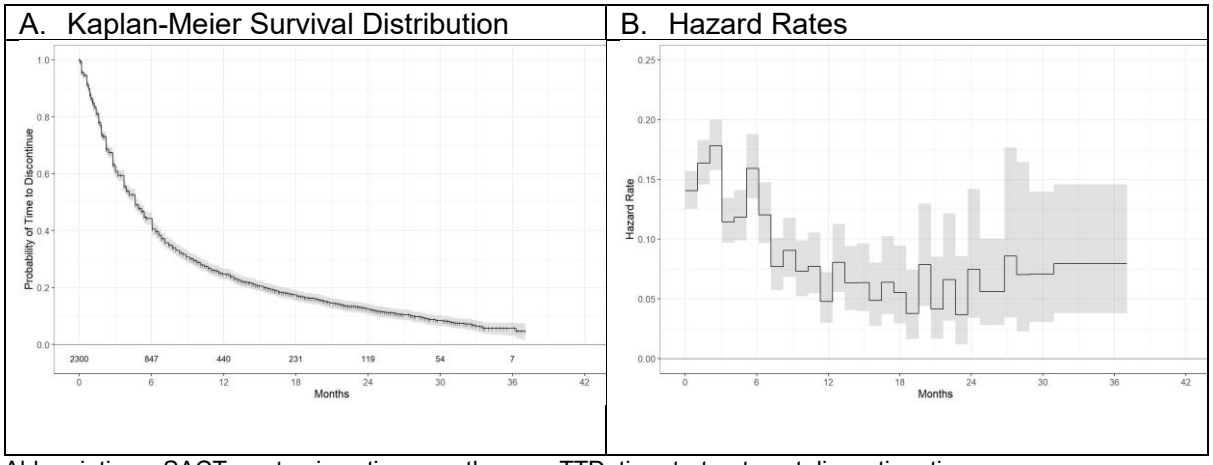
Abbreviations: Gen. generalised; IsaPd, isatuximab + pomalidomide + dexamethasone; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy; TTD, time-to-treatment discontinuation.

The log-normal distribution was used in the base case based on visual and statistical goodness of fit. The log-normal distribution yields projections of RMST for IsaPd time on treatment that is near the middle of the range of estimates from the various distributions considered. Although no external real-world data are available to validate the long-term projections, this distribution yields projection of TTD for IsaPd that are approximately 20% at six years, 10% at 14 years, and ~6% at 20 years. This choice can be considered conservative for IsaPd TTD as a longer time on treatment leads to higher medication costs as the combination is used for longer, and thus a more unfavourable comparison for IsaPd.

Daratumumab SACT

KM survival distribution and hazard rates for TTD for the daratumumab SACT population are reported in Figure 42.

Figure 42. TTD – daratumumab SACT Population



Abbreviations: SACT, systemic anti-cancer therapy; TTD, time-to-treatment discontinuation.

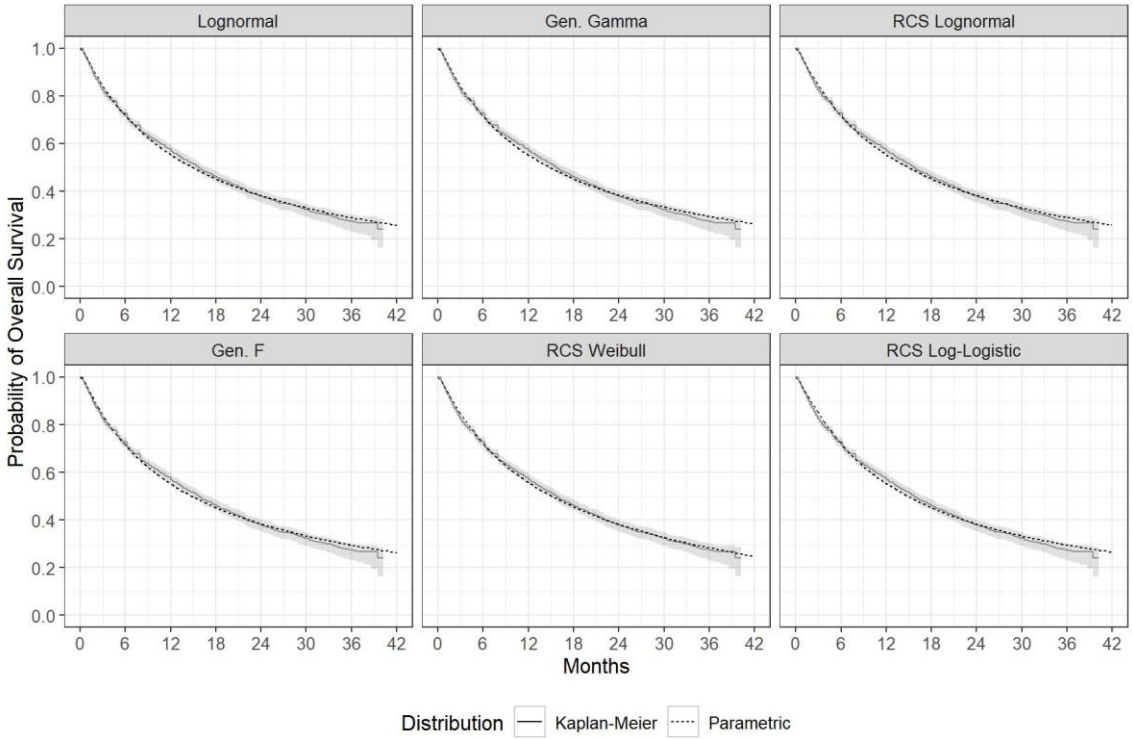
A ranking of parametric distributions fit to OS by the fit statistics are shown in Figure 43. The top six distributions, according to BIC statistic were as follows:

- Log-logistic
- RCS Weibull
- RCS log-normal
- Generalised gamma
- Log-normal
- RCS log logistic.

Parametric survival distributions for TTD during the follow up period for the six best fitting distributions based on BIC are shown in Figure 43 (distributions are ranked by BIC going left

to right, top to bottom). In visual inspection of the survival distributions, the generalised gamma has a very good fit to the KM curve.

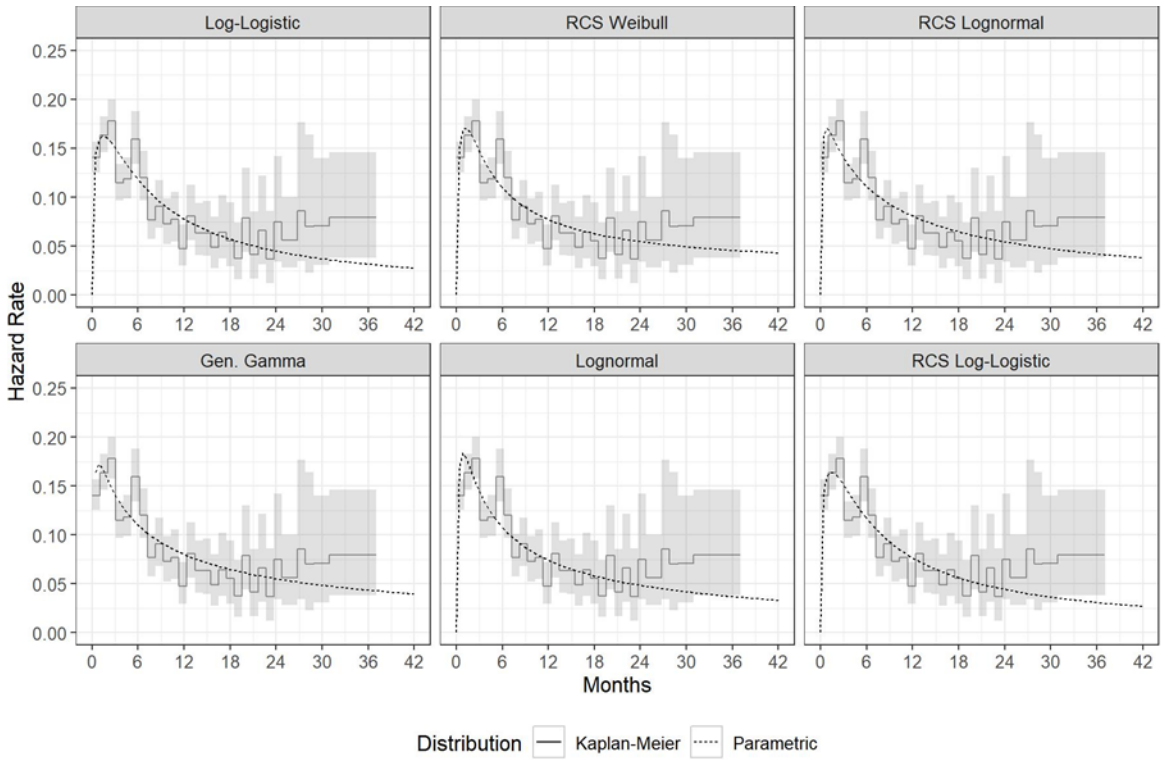
Figure 43. Parametric survival distributions fit to TTD – daratumumab SACT population



Abbreviations: Gen. generalised; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy; TTD, time-to-treatment discontinuation.

Hazard rates during follow-up for the top six best fitting parametric survival distributions based on BIC for OS are compared with non-parametric hazards in Figure 44. Long-term projections of OS (out to 20 years) for these six distributions are shown in Figure 45.

Figure 44. Hazard rates for parametric survival distributions fit to TTD – daratumumab SACT population



Abbreviations: Gen. generalised; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy; TTD, time-to-treatment discontinuation.

Figure 45. Long-term projections of TTD – daratumumab SACT population

[redacted]

Abbreviations: RCS, restricted cubic spline; SACT, systemic anti-cancer therapy; TTD, time-to-treatment discontinuation.

In TA783, the ERGs preferred distribution to fit to the daratumumab SACT TTD was the generalised gamma distribution (5). As such, the generalised gamma was used in the base case for the naïve SACT vs SACT analysis. The generalised gamma distribution also has a good visual and statistical goodness of fit and yields projections of RMST that are in the middle of the range of distributions (Appendix R).

IsaPd SACT and daratumumab SACT

The base case TTD distributions for IsaPd (lognormal) and daratumumab (generalised gamma) and the KM from the respective SACT datasets over the modelled time horizon are presented in Figure 46.

Figure 46. IsaPd and daratumumab SACT TTD KM curves and base case distributions

Abbreviations: KM, Kaplan-Meier; IsaPd, isatuximab + pomalidomide + dexamethasone; SACT, Systemic Anti-Cancer Therapy dataset; TTD, time to discontinuation.

B.3.3.3. General population mortality

Age- and sex-matched general population mortality values were derived from 2018–2020 UK lifetables, reported by the Office for National Statistics (ONS) (160). It was assumed that the probability of death in any given model cycle implied by the chosen OS distribution could not be less than that for the age- and sex-matched general population.

B.3.3.4. Adverse events

Grade ≥3 AEs with an incidence of 5% or more reported in either arm of the 4th line subgroup in the ICARIA-MM trial were included in the model. AE data for daratumumab was derived from TA510/783, as presented in Mateos 2020, for patients receiving daratumumab via subcutaneous injection (SC), given that the majority of daratumumab monotherapy given in clinical practice now is as SC (111). AE data for patients receiving daratumumab SC at 4th line specifically were not reported (5, 77). AE data used in the model base case are presented in Table 33. A scenario is included where patients receive isatuximab via SC injection. In this scenario adverse events are taken from the Quach 2022 study (156).

Table 33. Proportion of patients with grade ≥3 AEs in ≥5% of patients

Adverse event	IsaPd 4th line†	Pd (4th line population)†	Isatuximab subcutaneous formulation (scenario)†	Daratumumab monotherapy (5)
Acute kidney injury	3.8%	5.2%	0%	1.5%
Anaemia	0%	0%	10.0%	13.1%
Fatigue	5.8%	0%	0%	0.8%
Febrile neutropenia	13.5%	6.9%	20.0%	1.2%
Hypercalcaemia	1.9%	5.2%	0%	0%
Hypokalemia	0%	0%	0%	0.4%
Lower respiratory tract infection	7.7%	0%	0%	1.5%
Lymphopenia	0%	0%	0%	5.0%
Nausea	0%	0%	0%	0.4%
Neutropenia	46.2%	32.8%	70.0%	13.1%
Pneumonia	21.2%	24.1%	0%	2.7%
Thrombocytopenia	9.6%	10.3%	0%	13.8%

†Internal company analysis.
Abbreviations: AE, adverse event; Dara, daratumumab; IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone.

B.3.4. Measurement and valuation of health effects

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

In ICARIA-MM, EQ-5D-5L data were collected on Day 1 of each 28-day treatment cycle, at the end of treatment (EOT) visit and during the post-treatment follow-up period (60±5 days after last treatment administration).

B.3.4.2. Mapping

EQ-5D-5L data collected in ICARIA-MM, was cross-walked to EQ-5D-3L values using the mapping function developed by the NICE DSU using the Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU) dataset, and published as Hernández-Alava et al (161), as recommended by NICE in its updated methods guide.

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

An SLR was undertaken to identify relevant utility value data for patients with RRMM. For full details on the methods of the SLR and the identified studies, see Appendix H.

In the de novo SLR (October 2018) and first update (June 2019), a total of 20 studies (reported in 26 publications) were included in the review. In the update search conducted in November 2022, a total of 18 studies (reported in 20 publications), were included in the review. Taken together, 46 publications (1, 5, 26, 55, 77, 78, 112, 115, 116, 118, 130, 131, 133, 138, 139, 141, 144-147, 149-151, 153, 154, 162-182) were included across the de novo SLR and SLR update, reporting on 32 unique trials. The PRISMA flow diagram and a list of included studies and excluded studies is provided in Appendix H.

Aligned with the decision problem, the utility evidence submitted is focused on comparators relevant for people who have had three prior therapies only (4th line) or on UK studies, Pd and daratumumab monotherapy. A total of eight studies (reported in 12 publications) (1, 5, 26, 55, 77, 78, 112, 118, 130, 153, 154, 166) were relevant to the NICE decision problem for this reappraisal.

Of the four NICE appraisals (reported in eight publications) identified in the review (1, 5, 26, 55, 77, 78, 112, 118, 144-147), the most recent and relevant appraisals, pomalidomide [TA427] (55, 78), and daratumumab monotherapy [TA510/TA783] (5, 77, 112, 118) have been used to inform some model inputs, as both pomalidomide and daratumumab monotherapy have been recommended by NICE are treatment options for 4th line.

An overview of the utilities for patients with RRMM reported in the included studies relevant to the decision problem are provided in Appendix H.

B.3.4.4. Health-related quality-of-life data used in the cost-effectiveness analysis

Health state utility values for use in the model were estimated using generalised estimating equations (GEE) regression (an extension of generalised linear model [GLM] regression to adjust for clustering of data) (Table 34). Patients could contribute multiple observations to the analysis. Patients with a baseline assessment and at least one post-baseline assessment were included in the analysis.

Utilities were categorised by health state, with stratification on treatment and on vs off therapy and proximity to death (within 84 days of death). The 84-day (i.e. 12-week) period over which the 'terminal' 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 to allow robust estimation of the terminal utility decrement.

GEE regressions were conducted using the SAS PROC GENMOD procedure with the REPEATED statement and using an identity link function, normal error term distribution, and exchangeable correlation structure. Regressions including a variety of different health state variables were evaluated.

Table 34. GEE regression models considered for utility value estimation

Model	Health state covariate									Near Death
	IsaPd PFS	Pd PFS	PPS	IsaPd PFS On Tx	IsaPd PFS Off Tx	Pd PFS On Tx	Pd PFS Off Tx	PPS On Tx	PPS Off Tx	
1	X	X	X							
2	X	X	X							X
3			X	X	X	X	X			
4			X	X	X	X	X			X
5				X	X	X	X	X	X	
6				X	X	X	X	X	X	X

Abbreviations: GEE, generalised estimating equations; IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; PFS, progression-free survival; PPS, post-progression survival; Tx, treatment.

To control for differences between arms in the baseline utility values, utility values for the model were estimated based on least square mean (LSM) values which were estimated using the pooled mean baseline utility values for the two treatment arms combined. LSM utility values based on the different regression models are presented in Table 35.

Table 35. LSM EQ-5D-3L utility values based on alternate regression models for 4th line population†

Model	Value	Health State Covariate									Near Death
		IsaPd PFS	Pd PFS	PPS	IsaPd PFS On Tx	IsaPd PFS Off Tx	Pd PFS On Tx	Pd PFS Off Tx	PPS On Tx	PPS Off Tx	
1	Estimate	[redacted]									
1	Lower 95% CI	[redacted]									
1	Upper 95% CI	[redacted]									
2	Estimate	[redacted]									
2	Lower 95% CI	[redacted]									
2	Upper 95% CI	[redacted]									
3	Estimate	[redacted]									
3	Lower 95% CI	[redacted]									
3	Upper 95% CI	[redacted]									
4	Estimate	[redacted]									
4	Lower 95% CI	[redacted]									
4	Upper 95% CI	[redacted]									
5	Estimate	[redacted]									
5	Lower 95% CI	[redacted]									
5	Upper 95% CI	[redacted]									
6	Estimate	[redacted]									
6	Lower 95% CI	[redacted]									
6	Upper 95% CI	[redacted]									

†March 2022 data cut
Abbreviations: CI, confidence interval; IsaPd, isatuximab + pomalidomide + dexamethasone; LSM, least square mean; Pd, pomalidomide + dexamethasone; PFS, progression-free survival; PPS, post-progression survival; Tx, treatment.

Estimated LSM utility vales for PFS were slightly higher for IsaPd compared to Pd. Estimated utility values also were generally lower for patients off treatment rather than on treatment. The reason for this finding is uncertain but may reflect residual effects of AEs after discontinuation of study therapy due to toxicities or due to having stopped active treatment for their cancer. Estimated utility during PPS was on average less than that for PFS, though the PFS off treatment utilities were less than PPS off treatment utility. Assessment of this finding revealed that patients who experience time in the PFS off treatment state have poorer QoL and prognosis at baseline than those who spend time in other health states, and residence in this state is generally associated with Grade 3+ AEs, serious adverse events (SAEs), and terminal disease. Model 2 was used in the base case cost-effectiveness model as it aligned to the ERG and committee's preferred assumptions in the original appraisal for IsaPd [TA658] where the utilities values are same in on and off-treatment states for PFS or PPS (Table 36).

Table 36. EQ-5D-3L utility values used in model for 4th line population mapped from EQ-5D-5L for IsaPd and Pd (model 2)

State	Utility Value (95% CI)
PFS On Treatment (IsaPd)	[redacted]
PFS Off Treatment (IsaPd)	[redacted]
PFS On Treatment (Pd)	[redacted]
PFS Off Treatment (Pd)	[redacted]
PPS On Treatment	[redacted]
PPS Off Treatment	[redacted]
Terminal Decrement (12 weeks prior to death)	[redacted]

Abbreviations: CI, confidence interval; IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; PFS, progression-free survival; PPS, post-progression survival.

For patients that die from the PFS health state, the terminal decrement was applied to the PFS off treatment utility value. The proportion of PFS events that were death were [redacted] and [redacted] in the IsaPd and Pd arm, respectively, based on data from ICARIA-MM.

Since no utility data was available for daratumumab monotherapy from the ICARIA-MM trial, nor collected in the single arm trials that studied daratumumab monotherapy, utility values for daratumumab were assumed to be the same as Pd. This assumption is based on the fact that these two treatments have similar PFS in clinical practice and are therefore likely to have a similar utility (HRQoL impact) for the PFS health state. The utility values were adjusted for the differences in the incidence of AEs as described in Section B.3.3.4 and a disutility was also applied to account for the loss in quality of life as a result of AEs experienced during treatment with daratumumab monotherapy. The utility values used in

TA510/TA783 (5, 77, 112, 118) were taken from the Pd submission [TA427] (55, 78) and were lower than the utility value used in the current model for daratumumab monotherapy. Therefore, the use of Pd PFS health state utility value for the daratumumab monotherapy PFS state can be considered a conservative choice. Scenario analysis was considered where the utility values derived from TA510/TA783 (5, 77, 112, 118) have been used for daratumumab monotherapy to test the impact of this assumption on the total QALYs and the ICER. A summary of the utility values used in the analysis are presented in Table 37.

Table 37. Summary of utility values for base case cost-effectiveness analysis

State	Utility value: mean (SE)	95% CI	Reference in submission (section and page number)	Justification
PFS On Treatment (IsaPd)	[redacted]	[redacted]	Section B.3.4.4, Page 136	Utility values for IsaPd and Pd were derived from the ICARIA-MM trial EQ-5D-5L mapped to 3L as per the NICE reference case using the mapping function developed by the NICE Decision Support Unit using the "EEPRU" dataset, and published as Hernández-Alava et al. The utility values in PFS state for daratumumab monotherapy were assumed to be the same as those for Pd. This is a reasonable assumption as these two treatments have similar PFS in clinical practice and are therefore likely to have a similar utility (HRQoL impact). Scenario analysis will be considered where the PFS utility value for daratumumab monotherapy used in TA510 have been used (0.61) to test the impact of this assumption on the QALYs gained and the ICER.
PFS Off Treatment (IsaPd)	[redacted]	[redacted]		
PFS On Treatment (Pd and daratumumab monotherapy)	[redacted]	[redacted]		
PFS Off Treatment (Pd and daratumumab monotherapy)	[redacted]	[redacted]		
PPS On Treatment (all treatments)	[redacted]	[redacted]		
PPS Off Treatment (all treatments)	[redacted]	[redacted]		
Terminal Decrement (12 weeks prior to death)	[redacted]	[redacted]		
Acute kidney injury	0.37 (0.10)	0.17, 0.57	Section B.3.4.5, Page 141	Estimates for utility decrements (disutility) were derived from previous submissions to NICE where possible, and from literature.
Anaemia	0.31 (0.06)	0.19, 0.43		
Fatigue	0.12 (0.02)	0.08, 0.16		
Febrile neutropenia	0.39 (0.08)	0.23, 0.55		
Hypercalcaemia	0.04†	0.07, 0.09		
Hypokalemia	0.20†	0.15, 0.25		
Lower respiratory tract infection	0.19 (0.04)	0.11, 0.27		
Lymphopenia	0.07 (0.01)	0.05, 0.09		
Nausea	0.10†	0.08, 0.13		
Neutropenia	0.15 (0.03)	0.09, 0.21		
Pneumonia	0.19 (0.04)	0.11, 0.27		
Thrombocytopenia	0.31 (0.06)	0.19, 0.43		

† 25% standard deviation on the mean is assumed.
Abbreviations: CI, confidence interval; ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; NICE, National Institute for Health and Care Excellence; Pd, pomalidomide + dexamethasone; PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year; SE, standard error.

B.3.4.5. Adverse reactions

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 given that the EQ-5D data are collected on day 1 of each cycle.

For daratumumab, QALYs were adjusted for differences in the rates of AEs between Pd and daratumumab. While the same utility value for Pd and daratumumab captures the comparable efficacy in the PFS; these treatments have difference side-effect profiles. The overall AE decrement for daratumumab was calculated as the sum product of:

1. The difference in the rates of each AE between IsaPd and daratumumab
2. The corresponding disutility associated with each AE
3. The expected duration of each AE.

Estimates of the disutilities associated with Grade 3/4 AEs were based on values reported in the TA510 (183), TA171, and the literature (1, 5, 184-189). TA510 (5, 183) and TA171 (190) did not report a disutility value for hypercalcaemia, therefore a general disutility for any Grade 3/4 AEs that was used in the Institute for Clinical and Economic Review assessment of treatments for RRMM was used (36). The duration of disutility were based on values used in TA510 (183). An AE duration of 28 days was assumed where no data were available. A scenario is included in the model that uses duration of AEs as per key opinion leader (KOL) feedback obtained during the TA658 appraisal. The estimated duration and disutility for each AE included in the model are summarised in Table 38.

Table 38. Disutilities associated with Grade 3/4 AEs†

AE	Disutility	Duration (days) – base case	Source	Duration (days) – KOL feedback scenario
Acute kidney injury	0.37	28	Mistry 2018 (187)	28
Anaemia	0.31	180	TA510 (183) Brown 2013 (189) TA171 (190)	28
Fatigue	0.12	28	TA510 (183) Lloyd 2006 (188)	20.33
Febrile neutropenia	0.39	28	TA510 (183) TA658 (1)	16.33
Hypercalcaemia	0.04	28	TA510 (183) Institute for Clinical and Economic Review (ICER) (36)	28
Hypokalemia	0.20	0	TA510 (183)	0
Lower respiratory tract infection	0.19	7	Brown 2013 (189)	7
Lymphopenia	0.07	28	TA510 (183)	0
Nausea	0.10	28	TA510 (183) Lloyd 2006 (188)	28
Neutropenia	0.15	28	TA510 (183) Brown 2013 (189) TA171 (90)	59.63
Pneumonia	0.19	7	TA510 (183) Brown 2013 (82) TA171 (90)	9.17
Thrombocytopenia	0.31	28	TA510 (183) Brown 2013 (189) TA171 (90)	33.88

†Only grade 3/4 AEs relevant to both comparisons are presented.
Abbreviations: AE, adverse event; KOL, key opinion leader; NICE, National Institute for Health and Care Excellence.

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

B.3.5.1. Resource identification, measurement and valuation of 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 I.

In the de novo SLR (October 2018) and first update (June 2019), a total of 41 studies (reported in 53 publications) included in the review. In the update search conducted in November 2022, a total of 31 studies (reported in 34 documents) were included. Overall, a total of 87 publications were included across the de novo SLR and SLR update, reporting on

72 unique trials (1, 5, 26, 55, 77, 78, 102, 112, 118, 130-135, 138-141, 143-147, 149-154, 171, 176, 177, 191-244). The PRISMA flow diagram is provided in Appendix I.

Thirteen studies (reported in 19 publications) were carried out in the UK, including 12 HTAs: six NICE assessments (1, 5, 26, 55, 77, 78, 112, 118, 144-147), five SMC evaluations (150-154), one AWMSG (130) assessment, and a published study (191). Of the six NICE appraisals identified in the review (1, 5, 26, 55, 77, 78, 112, 118, 144-147), the most recent and relevant appraisals, were pomalidomide [TA427] (55, 78), and daratumumab monotherapy [TA510/TA783] (5, 77, 112, 118) as both have been recommended by NICE as treatment options for 4th line setting.
The appraisal of daratumumab monotherapy [TA510] (112, 118) was used to inform the original model for TA658 (1, 26) and these costs have been updated to reflect the latest prices for inflation or more recent costs have been used.

A summary of identified studies is provided in Appendix I.

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

B.3.5.2.1. Acquisition costs

Acquisition costs were taken from electronic market information tool (eMIT), where available, and the British National Formulary (BNF) (Table 39). A confidential PAS discount of [redacted] agreed with the Department of Health and the Patient Access Schemes Liaison Unit (PASLU) is applied to the list price of isatuximab in the base case analysis. [redacted] (Appendix Q).

Table 39. Unit costs of medications

Drug	Cost per pack (£)	PAS Discount (%)	Units per pack	Mg per Unit	Reference
Isatuximab (PAS price)	[redacted]	[redacted]	1	100	–
Pomalidomide	£8,884.00	–	21	4	BNF (13)
Dexamethasone (oral)	£57.50	–	50	8	eMIT (245)
Daratumumab (SC injection)	£4,320.00	–	1	1800	BNF (13)

Abbreviations: BNF, British National Formulary; eMIT; Drugs and pharmaceutical electronic market information tool; IV, intravenous; PAS, patient access scheme; SC, subcutaneous.

Table 40. presents the dosing regimens for all treatments. The full cost of the regimen cycle applied at the beginning of the treatment cycle. Dosing information was taken from the SmPC for IsaPd, Pd and daratumumab (157, 246, 247). Vial wastage was applied to all BSA- and weight-based drugs in the base case to reflect UK clinical practice. A scenario is included that assumes no vial wastage. Acquisition costs were adjusted for relative dose intensity (RDI), based on differences between planned and actual doses received (Table 40.). For IsaPd and Pd, most recent data on RDI were obtained from ICARIA-MM, data for daratumumab monotherapy was obtained from the COLUMBA trial (111). A scenario is presented that takes Pd RDIs within the IsaPd combination from RWE (44).

Whilst we are aware that there are Patient Access Scheme (PAS) discounts available for other treatments, these agreements are confidential and not known to us, so cannot be included in the analysis. Results including assumptions regarding these PAS discounts can be found in Appendix Q.

Table 40. Intervention and comparator dosing regimen

Regimen	Drug	Number of cycles	Daily dose	Days dosed per cycle	Weeks per cycle	Maximum cycles	Relative dose intensity – base case	Relative dose intensity – RWE scenario (44)
IsaPd (30, 247)	Isatuximab	1	10 mg/kg	4	4	1	[redacted]†	–
		2+	10 mg/kg	2	4	–	[redacted]†	–
	Pomalidomide	All	4 mg/day	21	4	–	[redacted]†	[redacted]
	Dexamethasone	All	40 mg/day	4	4	–	[redacted]†	[redacted]
Pd (246)	Pomalidomide	All	4 mg/day	21	4	–	[redacted]†	–
	Dexamethasone	All	40 mg/day	4	4	–	[redacted]†	–
Daratumumab monotherapy (157)	Daratumumab	1-2	1800 mg	4	4	2	100% (111)	–
		3-6	1800 mg	2	4	4	100% (111)	–
		7+	1800 mg	1	4	–	100% (111)	–

†Internal company analysis.
Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone.

B.3.5.2.2. Administration costs

Administration costs were taken from NHS reference costs 2020/2021 (Table 41) and were assigned for every day of medication administration. As per feedback from an NHS pharmacist obtained during the initial appraisal, for combination regimens, administration costs were calculated as the maximum administration cost of any component in the combination. For pomalidomide, SB11Z code is used for the first dose only. Subsequent doses of pomalidomide were assumed to incur zero cost, as this is an oral treatment.

Table 41. Administration costs

Type of administration	NHS reference code (248)	Cost
Oral, first dose	SB11Z	£215.80
Oral, subsequent dose(s)†	–	£0.00
Injection, first dose	SB12Z	£281.11
Injection, subsequent dose(s)	SB12Z	£281.11
IV, first dose	SB13Z	£258.56
IV, subsequent dose(s)	SB15Z	£438.38
IV, prolonged first dose‡	SB14Z	£526.26

† Assumption; ‡ Prolonged first dose computed using average of values reported for chemotherapy: outpatient and chemotherapy (daycase and reg day/night).
Abbreviations: IV, intravenous; NHS, National Health Service.

B.3.5.2.3. Pre-medication

Patients receiving treatment with IsaPd, Pd, and daratumumab monotherapy require pre-medication. Pre-medication regimens and costs are presented in Table 42 and Table 43, respectively, as per the relevant SmPC. Consistent with assumptions made in the economic model in the manufacturer's submission to NICE for daratumumab, patients receiving Pd were assumed to receive acetylsalicylic acid with every dose of Pd, as anticoagulation therapy (118). Pre-medication for daratumumab is assumed to be delivered with every dose of daratumumab. Dexamethasone pre-medication for IsaPd is not costed as it is assumed to be included in the dexamethasone dose in IsaPd as per the SmPC. Pre-medications are not a significant contributor to the overall costs, relative to the costs of other medications, but have been included in the model for completeness. Unit costs were taken from eMIT and BNF, as presented in Table 43.

Table 42. Pre-medication regimens

Regimen	Pre-medication drug	Dose (mg)	Doses per cycle
IsaPd†	Paracetamol	1000	Cycle 1: 4 Subsequent cycles: 2
	Cetirizine	50	Cycle 1: 4 Subsequent cycles: 2
	Acetylsalicylic acid‡	325	21
Pd	Acetylsalicylic acid	325	21
Daratumumab monotherapy	Methylprednisolone	100	Given with every dose of daratumumab
	Paracetamol	1000	
	Cetirizine	5	

† Dexamethasone is also received as a pre-medication for isatuximab however, this is assumed to be included in the dexamethasone dose in IsaPd; ‡ Note, acetylsalicylic acid a premedication associated with pomalidomide in IsaPd.
Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone.

Table 43. Pre-medication drug costs

Pre-medication drug	Cost/pack	Units/pack	Mg/unit	Reference
Paracetamol	£2.34	100	500	BNF (13)
Cetirizine	£0.78	30	10	BNF (13)
Acetylsalicylic acid	£0.21	28	75	eMIT (245)
Methylprednisolone	£48.32	20	100	eMIT (245)

Abbreviations: BNF, British National Formulary; eMIT, Drugs and pharmaceutical electronic market information tool.

B.3.5.2.4. Concomitant medication

Concomitant treatments are applied for all therapies. Frequencies, mean number of units and unit costs are presented in Table 44 and Table 45, respectively.

Estimates of the proportions of patients who receive concomitant medication and the mean numbers of units were derived from ICARIA-MM for IsaPd and Pd. Proportions of patients receiving concomitant treatments and the mean number of units for daratumumab were taken from TA510/TA783 (104, 112).

Table 44. Concomitant therapy proportions and number of units

Treatment	Proportion of patients			Number of units		
	IsaPd†	Pd†	Daratumumab (5)	IsaPd†	Pd†	Daratumumab (5)
GCSF	[redacted]	[redacted]	8%	[redacted]	[redacted]	1.00
RBC transfusion	[redacted]	[redacted]	30%	[redacted]	[redacted]	3.00
Platelet transfusion	[redacted]	[redacted]	10%	[redacted]	[redacted]	4.79

†Internal company analysis.
Abbreviations: GCSF, granulocyte colony-stimulating factor; IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; RBC, red blood cell.

Unit costs of concomitant medication were taken from the manufacturer's submission for daratumumab (112) and the NHS Blood and DTS pricing 2022/23 (249).

Table 45. Unit costs of concomitant treatments

Treatment	Unit cost (5, 250)	Reference
GCSF	£56.07	TA510, inflated to 2022 costs using the PSSRU inflation indices
RBC transfusion	£153.30	NHS Blood and DTS pricing 2022/23 (249)
Platelet transfusion	£240.90	NHS Blood and DTS pricing 2022/23 (249)

Abbreviations: GCSF, granulocyte colony-stimulating factor; RBC, red blood cell.

B.3.5.2.5. Subsequent therapies

Subsequent therapies for IsaPd, Pd and daratumumab are derived from SACT data (as described in Section B.2.3.2) to best reflect UK clinical practice. A total of 17% of patients who received IsaPd in the combined EAMS and CDF cohorts received a subsequent therapy in the SACT dataset. Only treatments that accounted for ≥2% of subsequent treatments in the combined cohort (N=123) were included in the model. In the combined cohort, 8 patients received 'Trial unspecified' subsequent therapy; this was not included in the calculations. The remaining subsequent therapies in each arm were reweighted to sum to 100%. The subsequent therapies that would be received after Pd in the real world were assumed to be similar to those received in SACT after IsaPd, as it reflects the treatment options available at 5th line if Pd was used as a 4th line treatment. Daratumumab subsequent therapy data is taken from the daratumumab SACT report as per TA783. Only treatments that accounted for ≥2% of therapies received were included in the analysis. Subsequent therapy proportions used in the model base case are presented in Table 46.

Table 46. Subsequent therapy proportions, SACT data

Treatment	IsaPd	Pd	Daratumumab
Bendamustine	3.15%	3.15%	3.49%
Bortezomib	4.20%	4.20%	1.27%
Bortezomib + panobinostat	61.91%	61.91%	28.22%
Cyclophosphamide + pomalidomide	1.05%	1.05%	7.72%
Cyclophosphamide	11.54%	11.54%	4.76%
Cyclophosphamide + thalidomide	4.20%	4.20%	1.80%
Melphalan	10.49%	10.49%	3.81%
Bendamustine + thalidomide	4.20%	4.20%	2.01%
Pomalidomide	2.10%	2.10%	84.24%
Belantamab	19.94%	19.94%	0.95%

Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; SACT, Systemic Anti-Cancer Therapy dataset.

A scenario is included in the comparison vs Pd that uses subsequent therapy treatments and proportions derived from the 4th line subgroup in ICARIA-MM vs Pd (Table 47). Due to the large number of different subsequent treatments received, subsequent treatments accounting for greater than 3% of all treatments received in the 4th line subgroup of ICARIA-MM were considered for inclusion.

Table 47. Subsequent therapy proportions from ICARIA-MM, 4th line population

Treatment	IsaPd†	Pd†
Bendamustine	[redacted]	[redacted]
Bortezomib	[redacted]	[redacted]
Carfilzomib	[redacted]	[redacted]
Daratumumab	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]
Etoposide	[redacted]	[redacted]
Lenalidomide	[redacted]	[redacted]
Melphalan	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]
Pomalidomide	[redacted]	[redacted]
Belantamab	[redacted]	[redacted]

†Internal company analysis.
Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone.

Unit costs of subsequent therapies were derived from eMIT, where possible, and the BNF (Table 48). All prices presented are list price and do not include the confidential PAS discounts in place for these therapies.

Table 48. Unit costs of subsequent therapies

Drug	Cost per pack	Units per pack	Mg per unit	Reference
Bendamustine	£82.89	5	100	eMIT (245)
Bortezomib	£762.38	1	3.5	BNF (13)
Carfilzomib	£1,056.00	1	60	BNF (13)
Daratumumab	£4,320.00	1	1800	BNF (13)
Cyclophosphamide	£8.33	1	500	eMIT (245)
Etoposide	£11.50	1	100	BNF (13)
Lenalidomide	£4,368.00	21	25	BNF (13)
Melphalan	£30.93	25	2	BNF (13)
Doxorubicin	£234.66	1	200	BNF (13)
Pomalidomide	£8,884.00	21	4	BNF (13)
Thalidomide	£298.48	28	50	BNF (13)
Panobinostat	£4,656.00	6	20	BNF (13)
Belantamab	£5,707.83	1	100	BNF (13)

Abbreviations: BNF, British National Formulary; eMIT; Drugs and pharmaceutical electronic market information tool.

Details on dosing for subsequent therapies are provided in Table 49. Average duration of treatment was estimated using data from a Kantar Health Study of treatments in 5th line RRMM in Western Europe (252). Due to lack of treatment duration data in 5th line for cyclophosphamide in the Kantar Health data, duration for 4th line cyclophosphamide treatment was used instead. Duration for etoposide and doxorubicin was assumed to be that of 5th line use of the DT-PACE regimen. For bortezomib, mean duration of treatment was from the manufacturer's submission to NICE for PanVd (253). The duration for bendamustine was taken from NHS regimen information sheets (254, 255). 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).

Table 49. Dosing and average duration of subsequent therapies

Drug		Daily dose	Days dosed per cycle	Weeks per cycle	Average duration (maximum cycles)
Bendamustine		60 mg/m^2	2	4	6
Bendamustine + thalidomide	Bendamustine	60 mg/m^2	2	4	9
	Thalidomide	100 mg/day	28	4	9
Bortezomib (256)		1.3 mg/m^2	4	3	7
Bortezomib + panobinostat	Bortezomib	1.3 mg/m^2	Cycles 1-8: 4 Cycles 9-16: 2	3	Cycles 1-8: 8 Cycles 9-16: 4
	Panobinostat	20 mg/day	6	3	12
Carfilzomib (257)		20 mg/m^2	2	4	1
Daratumumab		27 mg/m^2	4	4	1
Cyclophosphamide + pomalidomide	Cyclophosphamide	50 mg/day	21	4	19
	Pomalidomide	4 mg/day	21	4	19
Cyclophosphamide + thalidomide	Cyclophosphamide	50 mg/day	21	3	8
	Thalidomide	150 mg/day	21	3	8
Daratumumab (157)		1800 mg/day	4	4	2
Lenalidomide		25 mg/day	21	4	14
Melphalan		150 mg/m^2	4	6	4
Cyclophosphamide (5, 77)		450 mg/m^2	1	1	52
Etoposide (258)		40 mg/m^2	4	4	4
Lenalidomide (259)		25 mg/day	21	4	14
Melphalan (5, 77)		150 mg/m^2	4	6	4
Doxorubicin (258)		10 mg/day	4	4	4
Pomalidomide		4 mg/day	21	4	9
Belantamab		3.4 mg/kg	1	3	9

Abbreviations: BNF, British National Formulary; eMIT; Drugs and pharmaceutical electronic market information tool.

B.3.5.3. Health state unit cost and resource use

B.3.5.3.1. Follow-up and monitoring costs

The cost of follow-up and monitoring were applied to patients in the PFS on treatment, PFS off treatment and PPS health states. Follow-up and monitoring costs were applied once a month as per the original company submission based on KOL feedback (Table 50).

Table 50. Unit costs of follow-up and monitoring services

Service	Cost (248)
Physician visit	£214.56
Complete blood count test	£3.63
Biochemistry	£1.85

A scenario is presented using follow-up and monitoring frequencies from TA783/TA510 (5, 183), presented in Table 51.

Table 51. Follow-up and monitoring services, monthly frequency, scenario analysis.

Service	Frequency (monthly)			
	PFS on-treatment	PFS off-treatment	PPS on-treatment	PPS off-treatment
Physician visit	0.23	0.08	0	0.08
Complete blood count test	0.21	0.21	0.39	0.39
Biochemistry	0.19	0.19	0.33	0.33

Abbreviations: PFS, progression-free Survival; PPS, post-progression Survival.

B.3.5.3.2. Terminal Care costs

A one-off EoL care cost of £981.41 for patients with RRMM was estimated from TA427 and inflated to 2022 costs using the PSSRU inflation indices (55, 251).

B.3.5.4. Adverse reaction unit cost and resource use

Adverse event costs were taken from NHS reference costs 2020/21 and TA783 (5) and were applied to the proportion of patients in each treatment arm experiencing an event (Table 33). AE costs are presented in Table 52. The expected cost of AEs per patient were applied as a one-off cost at the start of treatment.

Table 52. Adverse event costs

Adverse event	Estimated cost	Reference
Acute kidney injury	£4,875.27	NHS reference costs 2020/21, Weighted average of: LA07H, LA07J, LA07K (248)
Anaemia	£799.71	NHS reference costs 2020/21, Weighted average of: SA04G, SA04H, SA04I, SA04J, SA04K, SA04L (248)
Fatigue	£774.11	Assumed equal to asthenia in TA783, inflated to 2022(5)
Febrile neutropenia	£7125.94	TA783, inflated to 2022 (5)
Hypercalcaemia	£4,002.42	NHS reference costs 2020/21, Weighted average of: "Elective inpatient: Weighted average KC05G, KC05H. Fluid or Electrolyte Disorders, with Interventions, with CC Score 5+, 0-4" and "Non elective short stay: Weighted average KC05G, KC05H. Fluid or Electrolyte Disorders, with Interventions, with CC Score 5+, 0-4"
Lower respiratory tract infection	£1,858.27	NHS reference costs 2020/21, Weighted average of: Elective inpatient: DZ22K, DZ22L, DZ22M, DZ22N, DZ22P, DZ22Q. Unspecified acute lower respiratory infection, Non-elective short stay: DZ22K, DZ22L, DZ22M, DZ22N, DZ22P, DZ22Q. Unspecified acute lower respiratory infection, and Non-elective long stay: DZ22K, DZ22L, DZ22M, DZ22N, DZ22P, DZ22Q. Unspecified acute lower respiratory infection (248)
Lymphopenia	£928.09	NHS reference costs 2020/21, Weighted average of: SA08G, SA08H, SA08J (248)
Neutropenia	£928.09	NHS reference costs 2020/21, Weighted average of: SA08G, SA08H, SA08J (248)
Pneumonia	£844.74	NHS reference costs 2020/21, Weighted average of: DZ11K, DZ11L, DZ11M, DZ11N, DZ11P, DZ11Q, DZ11R, DZ11S, DZ11T, DZ11U, DZ11V (248)
Thrombocytopenia	£1,150.97	NHS reference costs 2020/21, Weighted average of: SA12G, SA12H, SA12J, SA12K (248)

Abbreviations: NHS, National Health Service.

B.3.6. Severity

Whilst the introduction of a severity modifier is on the whole positive and more equitable, the way that the methods were implemented (opportunity cost-neutral for the NHS) means that whilst some other non-EoL medicines can now qualify for a modifier, some EoL medicines like IsaPd are now, at best, eligible for the lower severity modifier (1.2 modifier, ~£36K/QALY equivalent threshold) or no modifier at all. For IsaPd, this adds a further hurdle for an appraisal that is already extremely challenging given there is no framework for assessing branded combination medicines in the UK.

Sanofi internal analyses suggest that comparators Pd and daratumumab would not necessarily be cost-effective if reappraised today. The committee for the NICE appraisal for Pd [TA427] (55, 78) concluded that Pd met EoL criteria (vs bendamustine plus dexamethasone and conventional chemotherapy) but noted that the ICERs were at the upper end of the range normally considered cost-effective if EoL criteria were met. In the daratumumab appraisal, the committee noted that the ICERs for daratumumab compared with Pd varied widely, reflecting a high degree of uncertainty associated with the results. However, the committee agreed that daratumumab met the EoL criteria and the ICER was likely less than £50,000 per QALY gained.

For completeness, QALY shortfall calculations for IsaPd are presented in Table 53 to Table 55. The QALYs for standard of care therapies have been generated from the company economic model. A starting age of 65.1 years and a 51.8% male population is assumed as per the ICARIA-MM trial. Using the general population utility values per Hernandez et al. (161), patients without the disease have an expected (discounted) 13.78 life years and 10.75 QALYs remaining. Patients with the disease who receive Pd are expected to accrue [redacted] life years in the progression-free state with an associated [redacted] utility value, and [redacted] life years in the progressed health state with an associated utility value of [redacted]. Patients, therefore, have an expected [redacted] remaining QALYs in the model timeframe, leading to an absolute and proportional QALY shortfall of [redacted] and [redacted] respectively, resulting in a QALY weighting of 1.0 when Pd is considered the standard of care, with results taken from the ICARIA-MM trial. However, at the appraisal of daratumumab monotherapy [TA783], Pd was the main comparator and daratumumab monotherapy was considered more clinically and cost-effective at the £50,000 WTP threshold. Using the SACT data for daratumumab monotherapy (used to derive the efficacy estimate in TA783) and using the ERG's preferred assumptions for long-term survival distributions, treatment with daratumumab monotherapy will obtain a total of [redacted] life years and [redacted] QALYs. This

results in an absolute and proportional shortfall of [redacted] and [redacted], respectively and qualifying for a QALY weighting of 1.2. Based on the accepted evidence in TA783 for Pd and daratumumab monotherapy, the efficacy and QALYs derived for Pd should in theory be worse than those for daratumumab monotherapy and hence the comparison vs Pd should at a minimum qualify for a 1.2 modifier.

The results of this analysis lacks face validity, but the finding may in part be explained by the improved survival seen for patients receiving Pd in the ICARIA-MM trial (median OS: 17.71 months) compared with those included in the MM-003 trial (median OS: 11.9 months) and in RWE sources outside of SACT (median OS: 10.9 months) (45, 46). The MM-003 trial informed the effectiveness evidence for Pd in both its own appraisal [TA427] and daratumumab monotherapy appraisal where it was used in a MAIC [TA510/TA783]. Therefore, it is highly likely that if RWE data for Pd in SACT were available, the QALYs gained by patients receiving Pd in clinical practice would only be equivalent to or worse than those derived using SACT data for daratumumab (Table 55).

Taken together, Sanofi maintain that IsaPd should continue to be assessed at a cost-effectiveness threshold of £50,000/QALY, due to the process inequity for this appraisal, as expected at entry into CDF and the severe nature of RRMM at 4th line.

Table 53. Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Proportion male	51.8% (Table 31)	B.3.2.1
Starting age	65.1 (Table 31)	

Abbreviations: QALY, quality-adjusted life year.

Table 54. Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean	Discounted life years
Progression-free (Pd)	[redacted]	[redacted]
Progressed (Pd)	[redacted]	[redacted]
Progression-free (Daratumumab monotherapy)	[redacted]	[redacted]
Progressed (daratumumab monotherapy)	[redacted]	[redacted]

Abbreviations: Pd, pomalidomide and dexamethasone; QALY, quality-adjusted life year.

Table 55. Summary of QALY shortfall analysis

Comparator considered	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall (proportional)
Pd	10.750	[redacted]	[redacted]
Daratumumab monotherapy	10.750	[redacted]	[redacted]

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

B.3.7. Summary of base-case analysis inputs and assumptions

B.3.7.1. Summary of base-case analysis inputs

A summary of base-case analysis inputs is provided in Table 56.

Table 56. Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: 95% CI (distribution)	Reference to section in submission
Patient characteristics at baseline			
Age, years	65.1	Empirical distribution (bootstrapped)	Section B.3.2.1
Percentage male, %	51.8%	Empirical distribution (bootstrapped)	
Weight, kg	73.1	Empirical distribution (bootstrapped)	
Body surface area, m^2	1.8	Empirical distribution (bootstrapped)	
Measures of efficacy – IsaPd vs Pd			
Parametric distribution for PFS, IsaPd and Pd	RCS Weibull distribution	Empirical distribution (bootstrapped)	Section B.3.3.2.1.2.
Parametric distribution for PFS on treatment, IsaPd and Pd	Restricted log-logistic distribution	Empirical distribution (bootstrapped)	Section B.3.3.2.1.3.
Parametric distribution for OS, IsaPd and Pd	Restricted log-normal distribution	Empirical distribution (bootstrapped)	Section B.3.3.2.1.1.
Parametric distribution for TTD, IsaPd and Pd	Restricted log-normal distribution	Empirical distribution (bootstrapped)	Section B.3.3.2.1.4.
Measures of efficacy – IsaPd vs daratumumab			
Parametric distribution for OS IsaPd	Log-normal distribution	Empirical distribution (bootstrapped)	Section B.3.3.2.2.1.
Parametric distribution for OS daratumumab	Weibull distribution	Empirical distribution (bootstrapped)	
Parametric distribution for TTD IsaPd	Log-normal distribution	Empirical distribution (bootstrapped)	Section B.3.3.2.2.2.
Parametric distribution for TTD daratumumab	Generalised gamma distribution	Empirical distribution (bootstrapped)	
Frequency of grade ≥3 AEs (%) – IsaPd			
Acute kidney injury	4%	Empirical distribution (bootstrapped)	Section B.3.3.4
Anaemia	0%	Empirical distribution (bootstrapped)	
Fatigue	6%	Empirical distribution (bootstrapped)	
Febrile neutropenia	13%	Empirical distribution (bootstrapped)	
Hypercalcaemia	2%	Empirical distribution (bootstrapped)	
Neutropenia	46%	Empirical distribution (bootstrapped)	
Pneumonia	21%	Empirical distribution (bootstrapped)	
Thrombocytopenia	10%	Empirical distribution (bootstrapped)	
Lymphopenia	0%	Empirical distribution (bootstrapped)	
Lower respiratory tract infection	8%	Empirical distribution (bootstrapped)	
Frequency of grade ≥3 AEs (%) – Pd			
Acute kidney injury	5%	Empirical distribution (bootstrapped)	Section B.3.3.4
Anaemia	2%	Empirical distribution (bootstrapped)	
Fatigue	0%	Empirical distribution (bootstrapped)	
Febrile neutropenia	7%	Empirical distribution (bootstrapped)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: 95% CI (distribution)	Reference to section in submission
Hypercalcaemia	5%	Empirical distribution (bootstrapped)	
Neutropenia	33%	Empirical distribution (bootstrapped)	
Pneumonia	24%	Empirical distribution (bootstrapped)	
Thrombocytopenia	10%	Empirical distribution (bootstrapped)	
Lymphopenia	0%	Empirical distribution (bootstrapped)	
Lower respiratory tract infection	0%	Empirical distribution (bootstrapped)	
Frequency of grade ≥3 AEs (%) – daratumumab			
Acute kidney injury	0%	Empirical distribution (bootstrapped)	Section B.3.3.4
Anaemia	13%	Empirical distribution (bootstrapped)	
Fatigue	1%	Empirical distribution (bootstrapped)	
Febrile neutropenia	1%	Empirical distribution (bootstrapped)	
Hypercalcaemia	0%	Empirical distribution (bootstrapped)	
Neutropenia	13%	Empirical distribution (bootstrapped)	
Pneumonia	3%	Empirical distribution (bootstrapped)	
Thrombocytopenia	14%	Empirical distribution (bootstrapped)	
Lymphopenia	5%	Empirical distribution (bootstrapped)	
Lower respiratory tract infection	2%	Empirical distribution (bootstrapped)	
General population utility value regression coefficients			
Intercept	[redacted]	Lognormal	Section B.3.3.3
Covariate - Age vs female	[redacted]	Lognormal	
Covariate - Age coefficient	[redacted]	Lognormal	
Covariate - Age-squared coefficient	[redacted]	Lognormal	
Duration of AEs (days)			
Acute kidney injury	28	-	Section B.3.3.4
Anaemia	180	-	
Fatigue	28	-	
Febrile neutropenia	28	-	
Hypercalcaemia	28	-	
Neutropenia	28	-	
Pneumonia	7	-	
Thrombocytopenia	28	-	
Lymphopenia	28	-	
Lower respiratory tract infection	7	-	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: 95% CI (distribution)	Reference to section in submission
Utility value by health state – IsaPd			
On-Therapy Progression-Free	[redacted]	Empirical Distribution (SE: 0.018)	Section B.3.4.4
Off-Therapy Progression-Free	[redacted]	Empirical Distribution (SE: 0.095)	
On-Therapy Post-Progression	[redacted]	Empirical Distribution (SE: 0.03)	
Off-Therapy Post-Progression	[redacted]	Empirical Distribution (SE: 0.038)	
Terminal Decrement	[redacted]	Empirical Distribution (SE: 0.062)	
Utility value by health state – Pd			
On-Therapy Progression-Free	[redacted]	Empirical Distribution (SE: 0.021)	Section B.3.4.4
Off-Therapy Progression-Free	[redacted]	Empirical Distribution (SE: 0.048)	
On-Therapy Post-Progression	[redacted]	Empirical Distribution (SE: 0.03)	
Off-Therapy Post-Progression	[redacted]	Empirical Distribution (SE: 0.038)	
Terminal Decrement	[redacted]	Empirical Distribution (SE: 0.062)	
Utility value by health state - Daratumumab			
On-Therapy Progression-Free	[redacted]	Empirical Distribution (SE: 0.021)	Section B.3.4.4
Off-Therapy Progression-Free	[redacted]	Empirical Distribution (SE: 0.048)	
On-Therapy Post-Progression	[redacted]	Empirical Distribution (SE: 0.03)	
Off-Therapy Post-Progression	[redacted]	Empirical Distribution (SE: 0.038)	
Terminal Decrement	[redacted]	Empirical Distribution (SE: 0.062)	
Medication dosing regimen – IsaPd			Section B.3.5.2.1
Isatuximab: Cycle 1			
Dose, mg/kg	10	–	
Days dosed/week	4	–	
Weeks/cycle	4	–	
Maximum Cycles	1	–	
RDI, %	[redacted]	Normal	
Isatuximab: Cycle 2+			
Dose, mg/kg	10	–	
Days dosed/week	2	–	
Weeks/cycle	4	–	
Maximum Cycles	–	–	
RDI, %	[redacted]	Normal	
Pomalidomide: all cycles			
Dose, mg/day	4	–	
Days dosed/week	21	–	
Weeks/cycle	4	–	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: 95% CI (distribution)	Reference to section in submission
Maximum Cycles	–	–	
RDI, %	[redacted]	Normal	
Dexamethasone: all cycles			
Dose, mg/day	40	–	
Days dosed/week	4	–	
Weeks/cycle	4	–	
Maximum Cycles	–	–	
RDI, %	[redacted]	Normal	
Medication dosing regimen – Pd			
Pomalidomide: all cycles			
Dose, mg/day	4	–	
Days dosed/cycle	21	–	
Weeks/cycle	4	–	
Maximum Cycles	–	–	
RDI, %	[redacted]	Normal	
Dexamethasone: all cycles			
Dose, mg/day	40	–	
Days dosed/week	4	–	
Weeks/cycle	4	–	
Maximum Cycles	–	–	
RDI, %	[redacted]	Normal	
Medication dosing regimen - Daratumumab monotherapy			
Cycles 1-2			
Dose, mg/day	1800	–	
Days dosed/cycle	4	–	
Weeks/cycle	4	–	
Maximum Cycles	2	–	
RDI, %	100.00%	Normal	
Cycles 3-6			
Dose, mg/day	1800	–	
Days dosed/cycle	2	–	
Weeks/cycle	4	–	
Maximum Cycles	4	–	
RDI, %	100.00%	Normal	
Cycles 7+			
Dose, mg/day	1800	–	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: 95% CI (distribution)	Reference to section in submission
Days dosed/cycle	1	–	
Weeks/cycle	4	–	
Maximum Cycles	–	–	
RDI, %	100.00%	Normal	
Medication costs			
Isatuximab			Section B.3.5.2.1
Cost/pack (including PAS)	[redacted]	–	
PAS discount	[redacted]	–	
Units/pack	1	–	
Mg/unit	100	–	
Pomalidomide			
Cost/pack	£8,884.00	–	
PAS discount	0%	–	
Units/pack	21	–	
Mg/unit	4	–	
Dexamethasone (IV)			
Cost/pack	£23.99	–	
PAS discount	0%	–	
Units/pack	10	–	
Mg/unit	3.3	–	
Dexamethasone (oral)			
Cost/pack	£57.50	–	
PAS discount	0%	–	
Units/pack	50	–	
Mg/unit	8	–	
Daratumumab monotherapy (subcutaneous formulation)			
Cost/pack	£4,320.00	–	
PAS discount	0%	–	
Units/pack	1	–	
Mg/unit	1800	–	
Administration costs			
Oral, first dose	£215.80	Lognormal (SD: Mean 25%)	Section B.3.5.2.2
Oral, subsequent dose	£0.00	Lognormal (SD: Mean 25%)	
Injection, first dose	£281.11	Lognormal (SD: Mean 25%)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: 95% CI (distribution)	Reference to section in submission
Injection, subsequent dose	£281.11	Lognormal (SD: Mean 25%)	
IV, first dose	£258.56	Lognormal (SD: Mean 25%)	
IV, subsequent dose	£438.38	Lognormal (SD: Mean 25%)	
IV, prolonged first dose	£526.26	Lognormal (SD: Mean 25%)	
Premedication costs (per pack)			
Paracetamol	£2.34	–	Section B.3.5.2.3
Cetirizine	£0.78	–	
Acetylsalicylic acid	£0.21	–	
Methylprednisolone	£48.32	–	
Proportion of patients receiving concomitant treatment - IsaPd			Section B.3.5.2.4
GCSF	71%	–	
RBC transfusion	21%	–	
Platelet transfusion	12%	–	
Proportion of patients receiving concomitant treatment - Pd			
GCSF	52%	–	
RBC transfusion	41%	–	
Platelet transfusion	14%	–	
Proportion of patients receiving concomitant treatment - Daratumumab monotherapy			
GCSF	8%	–	
RBC transfusion	30%	–	
Platelet transfusion	10%	–	
Number of units of concomitant treatment received - IsaPd			
GCSF	5.03	–	
RBC transfusion	2.18	–	
Platelet transfusion	2.50	–	
Number of units of concomitant treatment received - Pd			
GCSF	6.43	–	
RBC transfusion	2.79	–	
Platelet transfusion	2.38	–	
Number of units of concomitant treatment received - Daratumumab monotherapy			
GCSF	1.00	–	
RBC transfusion	3.00	–	
Platelet transfusion	4.79	–	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: 95% CI (distribution)	Reference to section in submission
Concomitant medication unit costs			
GCSF	£56.07	–	Section B.3.5.2.4
RBC transfusion	£153.30	–	
Platelet transfusion	£240.90	–	
AE costs			
Acute kidney injury	£4,875.27	Lognormal (SD: Mean 25%)	Section B.3.5.4
Anaemia	£799.71	Lognormal (SD: Mean 25%)	
Fatigue	£784.24	Lognormal (SD: Mean 25%)	
Febrile neutropenia	£7,219.15	Lognormal (SD: Mean 25%)	
Hypercalcaemia	£4,002.42	Lognormal (SD: Mean 25%)	
Neutropenia	£928.09	Lognormal (SD: Mean 25%)	
Pneumonia	£844.74	Lognormal (SD: Mean 25%)	
Thrombocytopenia	£1,150.97	Lognormal (SD: Mean 25%)	
Lymphopenia	£928.09	Lognormal (SD: Mean 25%)	
Lower respiratory tract infection	£1,858.27	Lognormal (SD: Mean 25%)	
Follow-up costs			
Physician visit	£214.56	Lognormal (SD: Mean 25%)	Section B.3.5.3.1
Complete blood count test	£3.63	Lognormal (SD: Mean 25%)	
Biochemistry	£1.85	Lognormal (SD: Mean 25%)	
Follow-up frequencies - On-Therapy progression-free frequency per month (all therapies)			Section B.3.5.3.1
Physician visit	1	–	
Complete blood count test	1	–	
Biochemistry	1	–	
Follow-up frequencies - On-Therapy post-progression frequency per month (all therapies)			
Physician visit	1	–	
Complete blood count test	1	–	
Biochemistry	1	–	
Follow-up frequencies - Off-Therapy progression-free frequency per month (all therapies)			
Physician visit	1	–	
Complete blood count test	1	–	
Biochemistry	1	–	
Follow-up frequencies - Off-Therapy post-progression frequency per month (all therapies)			
Physician visit	1	–	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: 95% CI (distribution)	Reference to section in submission
Complete blood count test	1	–	
Biochemistry	1	–	
Proportion receiving subsequent treatments - IsaPd			
Bendamustine	3.15%	Empirical Distribution	Section B.3.5.2.5
Bortezomib	4.20%	Empirical Distribution	
Bortezomib + panobinostat	61.91%	Empirical Distribution	
Cyclophosphamide + pomalidomide	1.05%	Empirical Distribution	
Cyclophosphamide	11.54%	Empirical Distribution	
Cyclophosphamide + thalidomide	4.20%	Empirical Distribution	
Lenalidomide	0.00%	Empirical Distribution	
Melphalan	10.49%	Empirical Distribution	
Bendamustine + thalidomide	4.20%	Empirical Distribution	
Pomalidomide	2.10%	Empirical Distribution	
Belantamab	19.94%	Empirical Distribution	
Proportion receiving subsequent treatments - Pd			
Bendamustine	3.15%	Empirical Distribution	Section B.3.5.2.5
Bortezomib	4.20%	Empirical Distribution	
Bortezomib + panobinostat	61.91%	Empirical Distribution	
Cyclophosphamide + pomalidomide	1.05%	Empirical Distribution	
Cyclophosphamide	11.54%	Empirical Distribution	
Cyclophosphamide + thalidomide	4.20%	Empirical Distribution	
Lenalidomide	0.00%	Empirical Distribution	
Melphalan	10.49%	Empirical Distribution	
Bendamustine + thalidomide	4.20%	Empirical Distribution	
Pomalidomide	2.10%	Empirical Distribution	
Belantamab	19.94%	Empirical Distribution	
Proportion receiving subsequent treatments - Daratumumab monotherapy			
Bendamustine	3.49%	Empirical Distribution	Section B.3.5.2.5
Bortezomib	1.27%	Empirical Distribution	
Bortezomib + panobinostat	28.22%	Empirical Distribution	
Cyclophosphamide + pomalidomide	7.72%	Empirical Distribution	
Cyclophosphamide	4.76%	Empirical Distribution	
Cyclophosphamide + thalidomide	1.80%	Empirical Distribution	
Lenalidomide	0.00%	Empirical Distribution	
Melphalan	3.72%	Empirical Distribution	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: 95% CI (distribution)	Reference to section in submission
Bendamustine + thalidomide	2.01%	Empirical Distribution	
Pomalidomide	84.24%	Empirical Distribution	
Belantamab	0.95%	Empirical Distribution	
Subsequent treatment dosing - Bendamustine			
Daily dose, mg/m^2	60	–	
Days dosed/cycle	2	–	
Weeks/cycle	4	–	
Average duration number of cycles	6	–	
Subsequent treatment dosing - Bortezomib			
Daily dose, mg/m^2	1.3	–	
Days dosed/cycle	4	–	
Weeks/cycle	3	–	
Average duration number of cycles	7	–	
Subsequent treatment dosing – Bortezomib (Bortezomib + Panobinostat)			
Daily dose, mg/m^2	All cycles: 1.3	–	
Days dosed/cycle	Cycles 1-8: 4 Cycles 9-16: 2	–	
Weeks/cycle	All cycles: 3	–	
Maximum number of cycles	Cycles 1-8: 8 Cycles 9-16: 4	–	
Subsequent treatment dosing – Panobinostat (Bortezomib + Panobinostat)			
Daily dose, mg/day	20	–	
Days dosed/cycle	6	–	
Weeks/cycle	3	–	
Average duration number of cycles	12	–	
Subsequent treatment dosing – Cyclophosphamide (cyclophosphamide + pomalidomide)			
Daily dose, mg/day	50	–	
Days dosed/cycle	21	–	
Weeks/cycle	4	–	
Average duration number of cycles	19	–	
Subsequent treatment dosing – Pomalidomide (cyclophosphamide + pomalidomide)			
Daily dose, mg/day	4	–	
Days dosed/cycle	21	–	
Weeks/cycle	4	–	
Average duration number of cycles	19	–	
Subsequent treatment dosing - Cyclophosphamide			

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: 95% CI (distribution)	Reference to section in submission
Daily dose, mg/m^2	450	–	
Days dosed/cycle	1	–	
Weeks/cycle	1	–	
Average duration number of cycles	52	–	
Subsequent treatment dosing – Cyclophosphamide (cyclophosphamide + thalidomide)			
Daily dose, mg/day	50	–	
Days dosed/cycle	21	–	
Weeks/cycle	3	–	
Average duration number of cycles	8	–	
Subsequent treatment dosing – Thalidomide (cyclophosphamide + thalidomide)			
Daily dose, mg/day	150	–	
Days dosed/cycle	21	–	
Weeks/cycle	3	–	
Average duration number of cycles	8	–	
Subsequent treatment dosing – Lenalidomide			
Daily dose, mg/day	25	–	
Days dosed/cycle	21	–	
Weeks/cycle	4	–	
Average duration number of cycles	14	–	
Subsequent treatment dosing - Melphalan			
Daily dose, mg/m^2	150	–	
Days dosed/cycle	4	–	
Weeks/cycle	6	–	
Average duration number of cycles	4	–	
Subsequent treatment dosing – Bendamustine (Bendamustine + thalidomide)			
Daily dose, mg/m^2	60	–	
Days dosed/cycle	2	–	
Weeks/cycle	4	–	
Average duration number of cycles	9	–	
Subsequent treatment dosing – Thalidomide (Bendamustine + thalidomide)			
Daily dose, mg/day	100	–	
Days dosed/cycle	28	–	
Weeks/cycle	4	–	
Average duration number of cycles	9	–	
Subsequent treatment dosing - Pomalidomide			
Daily dose, mg/day	4	–	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: 95% CI (distribution)	Reference to section in submission
Days dosed/cycle	21	–	
Weeks/cycle	4	–	
Average duration number of cycles	9	–	
Subsequent treatment dosing - Belantamab			
Daily dose, mg/kg	3.4	–	
Days dosed/cycle	1	–	
Weeks/cycle	3	–	
Average duration number of cycles	9	–	
Subsequent treatment costs - Bendamustine			Section B.3.5.2.5
Cost/pack	£82.89	–	
Units/pack	5	–	
Mg/unit	100	–	
Subsequent treatment costs - Bortezomib			
Cost/pack	£762.38	–	
Units/pack	1	–	
Mg/unit	3.5	–	
Subsequent treatment cost - Panobinostat			
Cost/pack	£4,656.00	–	
Units/pack	6	–	
Mg/unit	20	–	
Subsequent treatment costs - Cyclophosphamide			
Cost/pack	£8.33	–	
Units/pack	1	–	
Mg/unit	500	–	
Subsequent treatment costs – Thalidomide			
Cost/pack	£298.48	–	
Units/pack	28	–	
Mg/unit	50	–	
Subsequent treatment costs - Lenalidomide			
Cost/pack	£4,368.00	–	
Units/pack	21	–	
Mg/unit	25	–	
Subsequent treatment costs - Melphalan			
Cost/pack	£30.93	–	
Units/pack	25	–	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: 95% CI (distribution)	Reference to section in submission
Mg/unit	2	–	
Subsequent treatment costs - Pomalidomide			
Cost/pack	£8,884.00	–	
Units/pack	21	–	
Mg/unit	4	–	
Subsequent treatment costs - Belantamab			
Cost/pack	£5,707.83	–	
Units/pack	1	–	
Mg/unit	100	–	
Terminal care cost	£981.41	–	Section B.3.5.3.2

Abbreviations: AE, adverse event; BSA, body surface area; CI, confidence interval; Dara, daratumumab; IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; Pd, pomalidomide + dexamethasone; PFS, progression-free survival; PPS, post-progression survival.

B.3.7.2. Assumptions

A summary of base case model assumptions are provided in Table 57.

Table 57. Assumptions used in the base case model

Area	Assumption	Justification
Time horizon	40 years	Approximates a lifetime time horizon
Model cycle length	1 week for first 20 years, 1 year for years 20-40	Weekly cycle lengths are sufficiently short to accurately capture clinical outcomes and differences in treatment administrations, with no need for a half cycle correction. Cycle length is increased after 20 years after the majority of costs and outcomes have occurred. Half cycle correction are employed during yearly cycles in the later stage of the model.
Discounting	3.5% annually for costs and outcomes	As per the NICE reference case.
Extrapolation	IsaPd vs Pd: TTD, PFS on treatment, PFS, and OS curves were extrapolated. Curve selections were based on best statistical fit and clinical face validity of predictions	As the ICARIA trial duration and SACT follow-up durations were insufficiently long to capture the full long-term benefits of IsaPd, survival was extrapolated beyond the end of trial follow-up. Survival extrapolations were estimated as per NICE DSU TSD 14 guidance (158).
	IsaPd vs daratumumab: OS and TTD curves from the IsaPd and daratumumab SACT were extrapolated independently. Curve selections were based on best statistical fit for IsaPd and the preferred ERG distribution in the daratumumab submission [TA783]	
Proportionality of hazards	IsaPd vs Pd: PH assumed to hold true for IsaPd vs Pd	No evidence of non-proportionality of hazards could be identified for Pd vs IsaPd for PFS or OS.
Treatment duration	IsaPd vs Pd: Extrapolated from ICARIA-MM for IsaPd and Pd.	TTD distributions were estimated based on the ICARIA-MM trial data.
	IsaPd vs daratumumab: Treatment duration from SACT used for daratumumab.	Data for treatment duration from daratumumab SACT was utilised in the absence of head-to-head data vs IsaPd. SACT data provides evidence of daratumumab efficacy in UK population at 4L.
Subsequent therapies	Subsequent therapies considered were the eleven most frequently received treatments, representing regimens accounting for ≥2% of all subsequent treatments from SACT. Proportions receiving subsequent therapies for IsaPd and daratumumab are taken from the respective SACT databases; Pd is assumed equal to IsaPd.	Subsequent therapy types and proportions were derived from SACT to best reflect UK clinical practice. As data for Pd was not collected in the SACT, it was assumed subsequent therapy proportions for Pd are identical to IsaPd. The frequencies were not reported by regimen; therefore, some patients may have received more than one medication, and some received no post-study

Area	Assumption	Justification
	Dosing regimens were derived from respective prescribing information and the average duration of therapy was based on data from Kantar Health for Western Europe (253)	treatment. Duration of these treatments were not captured in ICARIA-MM, and therefore, Kantar Health data was chosen as the best available estimate for typical clinical practice in the UK.
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 comparator regimens	This inclusion rule captures important AEs and is consistent with procedures utilised in several other RRMM submissions
Probability of death within PFS	The probability of death during PFS was taken from ICARIA-MM. For daratumumab, it was assumed to be the same as for IsaPd	Daratumumab trial reports did not report the probability that a PFS event results in death. Therefore, it was assumed to be the same as for IsaPd.
Utilities	IsaPd vs Pd: Utility values for IsaPd and Pd were taken from ICARIA-MM. IsaPd vs daratumumab: Utility values for daratumumab were assumed to be the same as those for Pd adjusted for incidence in AEs	Utility data were not available for daratumumab and therefore assumed to be the same as those for Pd, given they have a similar median PFS. To differentiate between IsaPd and daratumumab utilities, daratumumab utility values were adjusted for AE incidence. It was assumed that any disutilities due to AEs for Pd and IsaPd are captured in EQ-5D data collected in ICARIA-MM. A scenario using the utilities assumed for daratumumab within TA510/TA783 is also provided.
Follow-up costs	Follow-up costs were assumed to be the same for all treatments	The frequencies and types of follow-up costs used in the model were based on clinical expertise in the UK 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 mortality probabilities for all treatments would not be less than that of the age- and sex-matched general population and that utility values for all treatments would not be greater than that of the age- and sex-matched general population.

Abbreviations: AE, adverse event; HR, hazard ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; NICE, National Institute for Health and Care Excellence; OS, overall survival; Pd, pomalidomide + dexamethasone; PH, proportional hazard; PSM, partitioned survival model; PFS, progression-free survival; QALY; quality-adjusted life year; RRMM, relapsed and refractory multiple myeloma; TTD, time to discontinuation; UK, United Kingdom.

B.3.8. Base-case results

B.3.8.1. Base-case incremental cost-effectiveness analysis results vs Pd

Base case results are presented in Table 58. These analyses are presented considering the PAS discount for isatuximab only, all other therapies are assumed to be at list price and therefore the results do not represent the actual cost effectiveness estimate for IsaPd vs Pd.

Due to challenges of demonstrating cost-effectiveness for combination therapies, such that IsaPd may not be cost-effective at a £0 cost for isatuximab, non-reference case analysis is also provided. The NICE manual states that 'In cases where a technology increases survival in people for whom the NHS is currently providing care that is expensive or would not be considered cost effective at NICE's normal levels, the committee may consider alongside the reference-case analysis a non-reference-case analysis with the background high-cost care removed'. This analysis is considered relevant as Pd was recommended at a price that resulted in an ICER range of between £45,000 to £49,000/QALY gained (vs VTd and conventional chemotherapy, respectively) and £143,000 per QALY 'lost' vs PanVd (55), it is unlikely that Pd would be deemed to be cost-effective by today's NICE methods (severity modifier, current SoC) (5, 55). Therefore, Table 58 presents the base case results removing the backbone cost of Pd in the IsaPd arm in the period in which patients are receiving Pd in both arms. A further analysis which takes into account the [redacted] and assumed discounts on other comparators and post-study treatments have been provided as a confidential appendix for illustration (Appendix Q).

Pomalidomide patent expiry is expected in Q2 2024, after which it is expected that the price of pomalidomide will significantly fall. Sanofi internal analyses estimate a [redacted] price erosion on generic entry. Therefore, base case results assuming a [redacted] discount to the list price of pomalidomide to estimate the cost-effectiveness of IsaPd when a generic version of pomalidomide may be available are presented in Table 60.

The ICERs reported also do not take into account the substantial additional value provided to the NHS via the VPAS rebate, for which isatuximab is eligible. This represents an additional 26.5% rebate on net sales of the product in 2023.

Table 58. Base case results vs Pd

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pd	[redacted]	[redacted]	[redacted]	–	–	–	–
IsaPd	[redacted]	[redacted]	[redacted]	£184,947	1.513	1.117	£165,554

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; Pd, pomalidomide + dexamethasone; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 59. Base case results vs Pd – pomalidomide and dexamethasone backbone cost removed

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pd	[redacted]	[redacted]	[redacted]	–	–	–	–
IsaPd	[redacted]	[redacted]	[redacted]	£48,422	1.513	1.117	£43,344

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; Pd, pomalidomide + dexamethasone; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 60. Base case results vs Pd – generic pomalidomide available†

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pd	[redacted]	[redacted]	[redacted]	–	–	–	–
IsaPd	[redacted]	[redacted]	[redacted]	£76,483	1.513	1.117	£68,463

†Discount of [redacted] of pomalidomide assumed
Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; Pd, pomalidomide + dexamethasone; PAS, patient access scheme; QALYs, quality-adjusted life years.

B.3.8.2. Base-case incremental cost-effectiveness analysis results vs daratumumab monotherapy

Due to the absence of head-to-head data comparing IsaPd with daratumumab, a naïve comparison has been performed to satisfy the requirement of the re-issued NICE scope and is therefore, subject to uncertainty (Section B.3.3.2.2). Due to the different data sources informing the IsaPd arm in the comparisons vs Pd and daratumumab and the lack of SACT data for Pd, a fully incremental analysis was not possible.

Base case results vs daratumumab monotherapy are presented in Table 61. These analyses are presented considering the PAS discount for isatuximab only, all other therapies are assumed to be at list price and therefore, does not represent the true cost effectiveness estimate for IsaPd vs daratumumab monotherapy. As described in B.3.8.1, due to the challenges of demonstrating cost-effectiveness even at £0 cost for isatuximab, two non-reference case analyses have again been provided. The results vs daratumumab monotherapy removing the backbone cost of Pd are presented in Table 62. The results vs daratumumab assuming a [redacted] discount to the list price of pomalidomide are presented in Table 63. An analysis which takes in account assumed discounts on other comparators and post-study treatments have been provided as a confidential appendix (Appendix Q).

Table 61. Base case results vs daratumumab monotherapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Daratumumab	[redacted]	[redacted]	[redacted]	–	–	–	–
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£144,981

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years; WTP, willingness to pay.

Table 62. Base case results vs daratumumab monotherapy – pomalidomide and dexamethasone backbone cost removed

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER (£/QALY)
Daratumumab	[redacted]	[redacted]	[redacted]	–	–	–	–
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£61,407

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years; WTP, willingness to pay.

Table 63. Base case results vs daratumumab monotherapy– generic pomalidomide available†

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER (£/QALY)
Daratumumab	[redacted]	[redacted]	[redacted]	–	–	–	–
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,536

†Discount of [redacted] of pomalidomide assumed

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years; WTP, willingness to pay.

B.3.8.3. Applying a value attribution approach to cost-effectiveness of IsaPd vs Pd

The appraisal of pertuzumuab in breast cancer led NICE to commission a report on how to assess treatments that are not cost-effective at zero price in 2014 (9). Limited progress has been made since the issue was first identified nearly a decade ago with a resulting detrimental impact on access to many innovative combination therapies. The issue of valuing and paying for combination therapies has been discussed involving multiple stakeholders, yet currently there is no agreed solution (8). In addition to a mechanism to allow companies to negotiate the price of a combination (which is currently prohibited by competition law), methodologies have been proposed that would allow attribution of value to constituents of a combination therapy that could then be used to inform a value-based price for each of the constituents when used in combination. These methods apportion value using a weighting approach and incorporate the effectiveness of the combination in its totality and that of each component medicine used as a monotherapy (260, 261). Isatuximab in the IsaPd combination suffers from an imbalance in market power as pomalidomide is owned by a different manufacturer. Pomalidomide had the advantage of an earlier market entry, price setting and has already been assessed by NICE at the EoL threshold of £50,000/QALY (55). As Sanofi have no control or visibility of the price of pomalidomide, we have explored how value attribution may be applied to the IsaPd combination to demonstrate that isatuximab is available at a value-based price. In the absence of full information (no comparable data available for isatuximab as a monotherapy), we cannot be certain of the QALY relationship between the monotherapies and the combination- whether they are additive, strictly sub-additive or synergistic. For simplicity we assume that the combination of IsaPd is additive in line with the proposals laid out by Briggs et al (260).

To enable the application of methods proposed in the literature, dexamethasone QALYs were obtained from the appraisal for lenalidomide in combination with dexamethasone for a subgroup of patients who received two prior therapies (190). Since the patients who are eligible for IsaPd and Pd are required to be lenalidomide refractory, one might expect these patients to gain fewer QALYs with dexamethasone only treatment after three prior therapies that included lenalidomide. Given we have assumed an additive relationship, the discounted QALYs attributable to isatuximab as an add-on is therefore [redacted] (Table 64).

The value split of the combination was calculated using the following:

$$V(B) = \frac{H(B)}{H(B+A)}$$

$$V(A) = \frac{H(B+A) - H(B)}{H(B+A)}$$

Where V is the value split of a treatment, H is the incremental QALYs vs dexamethasone, B is Pd, and A is isatuximab. The proportion of the value of the combination therefore attributed to Pd is [redacted], and [redacted] is attributed to isatuximab.

Table 64. QALYs and costs attributable to isatuximab and Pd within the IsaPd combination

	Total QALYs (discounted)	Δ QALYs (vs dexamethasone)	Value (V) split (%)
Dexamethasone	0.77†	–	–
Pd (B)	[redacted]	[redacted]	[redacted]
Isatuximab (A)	[redacted]	–	[redacted]
IsaPd (B+A)	[redacted]	[redacted]	V(B+A) = 100%

†Data for dexamethasone absolute QALYs was obtained from the appraisal for lenalidomide in combination with dexamethasone vs dexamethasone in patients who received 2 prior therapies.
‡Data from Sanofi economic model for base case vs Pd
Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide and dexamethasone; QALY, quality-adjusted life year; WTP, willingness to pay.

In the base case analysis ([redacted] discount on isatuximab, list price for pomalidomide), isatuximab accounts for [redacted] of the total medication cost (discounted) associated with the IsaPd combination (Table 65). [redacted] (Table 65). [redacted]

Table 65. Combination cost scenarios at varying discounts for isatuximab and pomalidomide

	[redacted]		[redacted]		[redacted]	
	Discounted costs	**% total medication costs**	**Discounted costs**	**% total medication costs**	**Discounted costs**	**% total medication costs**
Total Isatuximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Premedication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total all therapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In the base case, threshold analysis demonstrates that to be cost-effective at a willingness to pay (WTP) threshold of £50,000 per QALY (assuming a discount of [redacted] is available on pomalidomide), total medication costs (discounted) for the combination would need to equal [redacted]. Applying the [redacted]% weighting to this derives an isatuximab total cost of [redacted]. Achieving this total cost requires a discount to the isatuximab list price of [redacted]. The PAS price of isatuximab can therefore be considered a value-based price.

B.3.9. Exploring uncertainty

B.3.9.1. Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. 1,000 Monte Carlo simulations were recorded, after which the ICER remains stable. Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution and results were plotted on a cost-effectiveness plane.

B.3.9.1.1. IsaPd vs Pd

Results of PSA of IsaPd vs Pd are presented in Table 66. The average incremental costs over the simulated results were £179,577 and the average incremental QALYs were 1.032, resulting in a probabilistic ICER of £174,026, when considering a PAS discount for isatuximab only. These results were highly congruent with the deterministic incremental costs of £184,973 and incremental QALYs of 1.117.

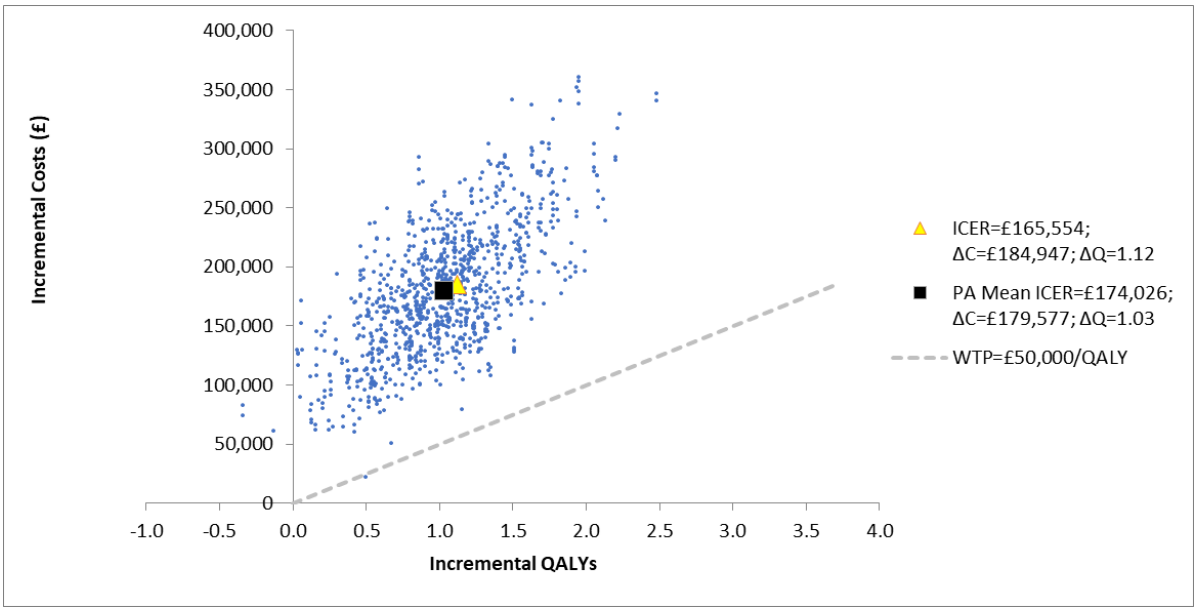
Table 66. Probabilistic sensitivity analysis results (IsaPd vs Pd)- PAS for isatuximab only

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Pd	[redacted]	[redacted]	-	-	-
IsaPd	[redacted]	[redacted]	£179,577	1.032	£174,026

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; Pd, pomalidomide + dexamethasone; PAS, patient access scheme; QALYs, quality-adjusted life years.

The scatter plot of simulations on the cost-effectiveness plane for IsaPd vs Pd is presented in Figure 47.

Figure 47. Scatter plot of simulations on cost-effectiveness plane (IsaPd vs Pd)



Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; PA, probabilistic analysis; Pd, pomalidomide + dexamethasone; WTP, willingness to pay.

PSA results for the non-reference case analyses, removing the backbone cost of pomalidomide and dexamethasone, and adjusting for the availability of generic pomalidomide are presented in Appendix T.

B.3.9.1.2. IsaPd vs daratumumab monotherapy

Results of PSA are presented in Table 67. The average incremental costs over the simulated results were [redacted] and the average incremental QALYs were [redacted], resulting in a probabilistic ICER of £146,336. These results were highly congruent with the deterministic incremental costs of [redacted] and incremental QALYs of [redacted].

Table 67. Probabilistic sensitivity analysis results (IsaPd vs daratumumab monotherapy)- PAS for isatuximab only

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Daratumumab	[redacted]	[redacted]	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	£146,336

†WTP threshold of £50,000 assumed.
Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone;

The scatter plot of simulations on the cost-effectiveness plane for IsaPd vs daratumumab monotherapy is presented in Figure 48. PSA results for the non-reference case analyses, removing the backbone cost of pomalidomide and dexamethasone, and adjusting for the availability of generic pomalidomide are presented in Appendix T.

Figure 48. Scatter plot of simulations on cost-effectiveness plane (IsaPd vs daratumumab monotherapy)

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; PA, probabilistic analysis; WTP, willingness to pay.

B.3.9.2. Deterministic sensitivity analysis

The results of deterministic sensitivity analysis vs Pd are presented in Figure 49. Parameters were varied by 95% confidence intervals where available, or +/- 25% of the mean value. As the two parameters with the greatest impact on results is the pomalidomide medication costs in IsaPd and Pd, it was pivotal to consider the alternative analysis considering patent expiry for pomalidomide (Section B.3.8).

Figure 49. Deterministic sensitivity analysis - IsaPd vs Pd

Abbreviations: CI, confidence interval; H, high (parameter value); IsaPd, isatuximab + pomalidomide + dexamethasone; IV, intravenous; L, low (parameter value); Pd, pomalidomide + dexamethasone; RDI, relative dose intensity.

The results of deterministic sensitivity analysis vs daratumumab monotherapy are presented in Figure 50. The parameter with the greatest impact on results were again the acquisition cost of pomalidomide. The discount rates and AE disutilities were also drivers for the cost-effectiveness.

Figure 50. Deterministic sensitivity analysis - IsaPd vs daratumumab monotherapy

Abbreviations: CI, confidence interval; Dara, daratumumab; H, high (parameter value); ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; L, low (parameter value); Pd, pomalidomide + dexamethasone.

B.3.9.3. Scenario analysis

B.3.9.3.1. Deterministic scenario analysis

Deterministic scenario analyses were performed to explore the impact of varying key structural assumptions on results. A summary of presented scenario analyses are provided in Table 68. The results consider the applicability of the PAS for isatuximab only, all other therapies are considered at list price.

Table 68. Scenario analyses assumptions

Scenario	Scenario assumptions	Base case assumptions
No medication wastage	Weight- and BSA-based drug vials can be shared between patients	Weight- and BSA-based drug vials cannot be shared between patients
Medical resource use from Daratumumab NICE submission	**On-Therapy Progression-Free Resource use** Physician visit: 23% Complete blood count test: 21% Biochemistry: 19% **Off-Therapy Progression-Free Resource Use** Physician visit: 8% Complete blood count test: 21% Biochemistry: 19% **On-Therapy Post-Progression Resource Use** Physician visit: 0% Complete blood count test: 39% Biochemistry: 33% **Off-Therapy Post-Progression Resource Use** Physician visit: 8% Complete blood count test: 39% Biochemistry: 33%	**On-Therapy Progression-Free, Off-Therapy Progression-Free, On-Therapy Post-Progression, Off-Therapy Post-Progression Resource use** Physician visit: 100% Complete blood count test: 100% Biochemistry: 100%
20-year time horizon	20-year time horizon captures the majority of differences between costs and outcomes	40-year time horizon
1.5% effectiveness discount rate	Outcomes are discounted at 1.5% annual rate (and costs discounted at 3.5%)	3.5% effectiveness discount rate
1.5% cost discount rate	Costs are discounted at 1.5% annual rate (and outcomes discounted at 3.5%)	3.5% cost discount rate
1.5% effectiveness and cost discount rates	Costs and outcomes are discounted at a 1.5% annual rate	3.5% cost and effectiveness discount rate

Scenario	Scenario assumptions	Base case assumptions
EQ-5D-5L utilities	**Progression-Free On- and Off-Treatment utility** IsaPd: [redacted] Pd: [redacted] Daratumumab: [redacted] **Post-progression On- and Off-Treatment utility** IsaPd: [redacted] Pd: [redacted] Daratumumab: [redacted] **Terminal decrement in utility** IsaPd[redacted] Pd:[redacted] Daratumumab:[redacted]	**Progression-Free On- and Off-Treatment utility** IsaPd: [redacted] Pd: [redacted] Daratumumab: [redacted] **Post-progression On- and Off-Treatment utility** IsaPd: [redacted] Pd: [redacted] Daratumumab: [redacted] **Terminal decrement in utility** IsaPd: [redacted] Pd: [redacted] Daratumumab: [redacted]
Isatuximab dosing based on ICARIA weight distribution	Isatuximab discount: [redacted] Based on separate calculations examining the cost difference when weight distribution vs. mean weight was used in isatuximab costing, it was found that using a weight distribution resulted in a[redacted] reduction in overall cost of isatuximab. This was implemented as a secondary discount after accounting for the PAS discount.	Isatuximab discount: [redacted] In the base case, mean weight was used for computing isatuximab dosing.
Pomalidomide and dexamethasone RDI in IsaPd combination based on RWE	Pomalidomide RDI: [redacted] Dexamethasone RDI: [redacted]	Pomalidomide RDI: [redacted] Dexamethasone RDI: [redacted]
Treatment discontinued upon progression, log-logistic (R) (best BIC)	IsaPd On-Treatment PFS: restricted log-logistic Pd On-Treatment PFS: restricted log-logistic	IsaPd TTD: restricted log-normal Pd TTD: restricted log-normal
Independently-fit OS for IsaPd (log-normal) and Pd (Weibull), (previous ERG preferred) (vs Pd only)	OS distributions IsaPd: Independent log-normal Pd: Independent Weibull	OS distributions IsaPd and Pd: restricted log-normal
Independently-fit OS for IsaPd (log-normal) and Pd (Exponential) (vs Pd only)	OS distributions IsaPd: Independent log-normal Pd: Independent exponential	OS distributions IsaPd and Pd: restricted log-normal
Exponential distribution for IsaPd and Pd OS (KOL Preferred) (vs Pd only)	OS distributions IsaPd and Pd: Joint Exponential	OS distributions IsaPd and Pd: restricted log-normal
No Dara Subsequent Tx – IPCW adjustment (vs Pd only)	IPCW adjustment to OS to adjust for subsequent treatment with daratumumab	No adjustment • IsaPd OS distribution: restricted lognormal

Scenario	Scenario assumptions	Base case assumptions
	• IsaPd OS distribution: restricted lognormal distribution • IsaPd vs Pd HR for OS: 0.650	
No Dara Subsequent Tx – TSE adjustment (vs Pd only)	TSE adjustment to OS to adjust for subsequent treatment with daratumumab • IsaPd OS distribution restricted lognormal distribution • IsaPd vs Pd HR for OS: 0.618	No adjustment • IsaPd OS distribution: restricted lognormal
Isatuximab administered as subcutaneous	Isatuximab administered as a subcutaneous formulation • Dose/administration: 1400 mg/day • RDI: [redacted] • Adverse event rates derived from Quach 2022 study (156)	Isatuximab administered as IV • Dose/administration: 10 mg/kg • RDI: [redacted] • Adverse event rates derived from ICARIA-MM
Subsequent therapies from ICARIA-MM	Subsequent therapy from fourth-line subgroup of ICARIA-MM (Table 47)	Subsequent therapy for IsaPd and daratumumab from respective SACT datasets, Pd subsequent therapies assumed identical to IsaPd SACT (Table 46)
Duration of AEs based on KOL feedback (vs daratumumab only)	AE durations based on KOL feedback presented in Table 38	AE durations from the literature
Dara administered as IV (vs daratumumab only)	Patients receive daratumumab 16 mg/kg infusion on days 1, 8, 15 and 22 of each cycle in Cycles 1-2, then days 1 and 15 of each cycle in Cycles 3-6, then day 1 of each cycle for subsequent cycle	1,800 mg injection every week for each 28-day cycle for Cycles 1–2, 1,800 mg injection every two weeks for each 28-day cycle for Cycles 3–6, 1,800 mg injection every four weeks for each 28-day cycle for Cycles 7+.
Utilities for Dara PFS from Dara NICE submission (vs daratumumab only)	PFS utility value, daratumumab: 0.61	PFS utility value, daratumumab: [redacted]
IsaPd TTD RCS Weibull (vs daratumumab only)	IsaPd TTD distribution: log-normal	IsaPd OS distribution: RCS Weibull
IsaPd TTD and OS both RCS Weibull (vs daratumumab only)	IsaPd OS and TTD distribution: log-normal	IsaPd OS and TTD distribution: RCS Weibull

Abbreviations: BIC, Bayesian Information Criterion; BSA, body surface area; Dara, daratumumab; HR, hazard ratio; IPCW, inverse probability censor weighting; IsaPd, isatuximab + pomalidomide + dexamethasone; IV, intravenous; KOL, key opinion leader; Pd, pomalidomide + dexamethasone; OS, overall survival; PFS, progression-free survival; RCS, restricted cubic spline; RDI, relative dose intensity; SACT, systemic anti-cancer therapy; TSE, two-stage adjustment; TTD, time to discontinuation; Tx, treatment.

The results of scenario analysis vs Pd are presented in Table 69.The biggest impact on the ICER was using the exponential distribution for IsaPd and Pd OS, which increased the ICER by 29%. Adjusting efficacy by removing the impact of subsequent daratumumab therapy reduced the ICER by 15% when using the IPCW method and 23% when using the TSE method. Assuming treatment continued until disease progression decreased the ICER by 3%. Using independently fitted curves for IsaPd and Pd overall had minimal impact on the ICER.

Table 69. IsaPd vs Pd deterministic scenario analysis

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)	% change from base case ICER
Base case	£184,947	1.117	£165,554	–
No medication wastage	£142,509	1.117	£127,566	-23%
Other costs from Dara NICE submission	£181,679	1.117	£162,628	-2%
20-year time horizon	£177,525	1.058	£167,729	1%
1.5% effectiveness discount rate	£184,947	1.286	£143,824	-13%
1.5% cost discount rate	£206,948	1.117	£185,248	12%
1.5% effectiveness and cost discount rates	£206,948	1.286	£160,933	-3%
EQ-5D-5L utilities	£184,947	1.095	£168,978	2%
Isatuximab dosing based on ICARIA weight distribution	£183,595	1.117	£164,344	-1%
IsaPd Pomalidomide and dexamethasone RDI based on RWE	£184,730	1.117	£165,360	0%
Treatment discontinued upon progression, log-logistic (R) (best BIC)	£180,156	1.117	£161,266	-3%
Independently-fit OS for IsaPd (Lognormal) and Pd (Weibull), (previous ERG preferred)	£185,425	1.070	£173,366	5%
Independently-fit OS for IsaPd (Lognormal) and Pd (Exponential)	£188,159	1.148	£163,930	-1%
Exponential distribution for IsaPd and Pd OS (KOL Preferred)	£175,329	0.822	£213,356	29%
No Dara Subsequent Tx – IPCW HR OS	£185,946	1.321	£140,713	-15%
No Dara Subsequent Tx – TSE HR OS	£186,607	1.461	£127,720	-23%
Isatuximab administered as subcutaneous	£176,024	1.117	£157,567	-5%
Subsequent therapies from ICARIA-MM	£228,129	1.117	£204,208	23%

Abbreviations: Dara, daratumumab; ERG, evidence review group; HR, hazard ratio; IPCW, inverse probability censor weighting; IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide and dexamethasone; OS, overall survival; R, restricted; RWE, real-world evidence; TSE, two-stage estimator; Tx, treatment.

Scenario analyses (Table 70) were also performed to explore the impact of varying key structural assumptions on results in the analysis vs daratumumab monotherapy. The scenario that had the biggest impact on the ICER was changing the OS and TTD distribution for IsaPd. An assumption of IsaPd long-term survival and discontinuation both using the RCS Weibull distribution resulted in an ICER of £190,448 vs daratumumab monotherapy. However, this is considered a pessimistic scenario, particularly for OS, due to the short follow up in SACT for IsaPd. Clinical experts consulted agreed that with longer follow-up, they would expect the tails of the IsaPd curve to perform better. The availability of newer regimens for triple class refractory patients may further improve outcomes in the long term compared with current SoC.

Table 70. IsaPd vs daratumumab monotherapy deterministic scenario analysis

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)	% change from base case ICER
Base case	[redacted]	[redacted]	£144,981	–
No medication wastage	[redacted]	[redacted]	£91,880	-37%
Duration of AEs based on KOL feedback	[redacted]	[redacted]	£147,381	2%
Other costs from Dara NICE submission	[redacted]	[redacted]	£141,638	-2%
20-year time horizon	[redacted]	[redacted]	£152,367	5%
1.5% effectiveness discount rate	[redacted]	[redacted]	£121,106	-16%
1.5% cost discount rate	[redacted]	[redacted]	£161,523	11%
1.5% effectiveness and cost discount rates	[redacted]	[redacted]	£134,924	-7%
EQ-5D-5L utilities	[redacted]	[redacted]	£146,006	1%
Isa dosing based on ICARIA weight distribution	[redacted]	[redacted]	£143,929	-1%
IsaPd pomalidomide and dexamethasone RDI based on RWE	[redacted]	[redacted]	£144,813	0%
Dara administered as IV	[redacted]	[redacted]	£140,293	-3%
Utilities for Dara PFS from Dara NICE Submission	[redacted]	[redacted]	£135,379	-7%
IsaPd TTD (RCS Weibull)	[redacted]	[redacted]	£112,854	-22%
IsaPd TTD and OS (both RCS Weibull)	[redacted]	[redacted]	£190,448	31%
Isatuximab administered as subcutaneous	[redacted]	[redacted]	£138,372	-5%

Abbreviations: AE, adverse event; Dara, daratumumab; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; Isa, isatuximab; IsaPd, isatuximab + pomalidomide + dexamethasone; IV, intravenous; PFS, progression-free survival; NICE, National Institute for Health and Care Excellence; OS, overall survival; RCS, restricted cubic splines; RDI, relative dose intensity; RWE, real world evidence; TTD, time-to-treatment discontinuation; Tx, treatment.

B.3.9.3.2. Probabilistic scenario analysis

Select scenario analyses were also tested probabilistically, in which probabilistic model results are generated for a particular set of parameter estimates or assumptions. The results are generated by running the probabilistic analysis, and assumptions regarding parameter sampling for each variable can be varied. These results have been presented for the comparison against Pd (Table 71) and daratumumab (Table 72) and only consider the PAS discount for isatuximab with all other therapies at list price.

Table 71. IsaPd vs Pd – Key probabilistic scenario analysis

Scenario	Incremental costs	Incremental QALYs	ICER (/QALY)	% change from base case ICER
Base case (probabilistic)	£179,577	1.032	£174,026	–
EQ-5D-5L utilities	£179,577	1.009	£177,934	2%
Treatment discontinued upon progression, log-logistic (R) (best BIC)	£167,884	1.032	£162,692	-7%
Isa dosing based on ICARIA weight distribution	£178,250	1.032	£172,740	-1%
IsaPd pomalidomide and dexamethasone RDI based on RWE	£179,577	1.032	£174,026	0%
Independently-fit OS for IsaPd (Lognormal) and Pd (Weibull), (previous ERG preferred)	£181,331	1.072	£169,108	-3%
Independently-fit OS for IsaPd (Lognormal) and Pd (Exponential)	£183,440	1.151	£159,353	-8%
Exponential distribution for IsaPd and Pd OS (KOL Preferred)	£169,462	0.797	£212,700	22%
No Dara Subsequent Tx – IPCW HR OS	£178,019	1.357	£131,159	-25%
No Dara Subsequent Tx – TSE HR OS	£181,418	1.463	£123,986	-29%
Subsequent therapies from ICARIA-MM	£220,659	1.032	£213,838	23%

Abbreviations: BIC, Bayesian information criterion; Dara, daratumumab; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPCW, inverse probability censoring of weighting; Isa, isatuximab; IsaPd, isatuximab + pomalidomide + dexamethasone, intravenous; KOL, key opinion leader; PFS, progression-free survival; QALY, quality-adjusted life year; OS, overall survival; RDI, relative dose intensity; RWE, real world evidence; TSE, two-stage estimator; Tx, treatment.

Table 72. IsaPd vs daratumumab monotherapy– Key probabilistic scenario analysis

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)	% change from base case ICER
Base case (probabilistic)	[redacted]	[redacted]	£146,336	–
EQ-5D-5L utilities	[redacted]	[redacted]	£147,237	1%
Isa dosing based on ICARIA weight distribution	[redacted]	[redacted]	£145,284	-1%
IsaPd pomalidomide and dexamethasone RDI based on RWE	[redacted]	[redacted]	£146,336	0%
IsaPd TTD and OS (both RCS Weibull)	[redacted]	[redacted]	£191,044	31%
Utilities for Dara PFS from Dara NICE Submission	[redacted]	[redacted]	£137,052	-6%
IsaPd TTD (RCS Weibull)	[redacted]	[redacted]	£114,354	-22%

Abbreviations: BIC, Bayesian information criterion; Dara, daratumumab; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; Isa, isatuximab; IsaPd, isatuximab + pomalidomide + dexamethasone; PFS, progression-free survival; NICE, National Institute for Health and Care Excellence; OS, overall survival; QALY, quality-adjusted life year; RCS, restricted cubic splines; RDI, relative dose intensity; RWE, real world evidence; TTD, time-to-treatment discontinuation; Tx, treatment.

B.3.10. Subgroup analysis

No further subgroup analyses were performed.

B.3.11. Benefits not captured in the QALY calculation

Novel combinations are becoming increasingly central to cancer treatment and the triplet regimen IsaPd combines treatments with multiple modes of actions, targeting the disease in a synergistic manner. Consequently, IsaPd provides improved disease control (compared with doublet [Pd] or daratumumab monotherapy alone), evidenced by the superior PFS outcomes for IsaPd versus Pd in ICARIA-MM, with median PFS in the IsaPd arm (12.39 months [95% CI; 7.425, 27.663]) in comparison with the Pd arm (6.54 months [95% CI; 4.468, 10.086]), and when naively comparing IsaPd and daratumumab monotherapy SACT datasets demonstrating increased median treatment duration for IsaPd (considered a proxy for PFS) (8.9 months [95% CI: 7.3, 10.8]) than that observed for daratumumab monotherapy (4.5 months [95% CI: 4.3, 4.9]). However, valuing combination therapies is challenging as there is no accepted framework to attribute the costs and utility between the components forming the combination based on the value that they bring to the overall combination. Applying emerging methods for value attribution to IsaPd (260), clearly demonstrates that the value of isatuximab is not captured by the reference case cost-effectiveness analysis.

Hope becomes increasingly relevant at later lines of therapy, where IsaPd is currently used in UK clinical practice, however, is not explicitly captured in generic QoL instruments that are used in QALY calculations. Independent statements provided by a patient during the consultation for the initial NICE appraisal for IsaPd, continue to remain relevant today. They had highlighted the physical and psychological burden patients and their carers experience, especially after a third relapse, where treatment options become limited. This is further supported by Boland et al (2013) (20) and Hulin et al (2017) (21), who highlighted the burden patients perceive to add to their friends and family in the form of lack of physical function, and a reliance on emotional and physical support. Patients have also noted the reassurance of knowing that ‘they have access to the best possible treatment to give them a few more months/years of life’ (1). Willingness to pay exercises in cancer patients have found a strong preference for the ‘hopeful gamble’ of a larger survival gain over the ‘safe bet’ with a narrower ‘spread’ of outcomes (262). Thus, the cost-effectiveness analysis does not take into account the potential psychological benefit to patients, carers and families of people with myeloma.

It is clear that patients do not want to feel abandoned at the end of their lives and time spent in remission/progression free is incredibly important to patients and carers alike. Continued access to IsaPd at 4th line therefore, provides a bridge therapy and hope for more effective 5th line treatments to become available for when patients eventually relapse with the disease.

B.3.12. Validation

B.3.12.1. Validation of cost-effectiveness analysis

Quality control of the economic model was performed by the model developers and by two health economists not involved in the development of the model. This included:

- Cell-by-cell checks of formulae
- Rebuilding of key sections of the model
- Logical tests
- A full audit of model inputs.

Clinical and cost effectiveness inputs (including long term survival extrapolations) were discussed with myeloma treating clinical experts in the UK during an advisory board, both as part of the initial NICE submission [TA658] and again in February 2023 to inform the current appraisal. Prior to the February 2023 advisory board, four experienced UK haematologists were asked to complete a pre-work questionnaire and assign weights to each of the OS survival distributions (assuming a joint modelling framework) assigning their probability that each curve reflected the true survival of patients in UK real-world practice. During the advisory board, these weights were discussed by the clinicians and a consensus ‘group weighting’ was agreed upon during the session. Further details are provided in the advisory board report (3). Feedback has been incorporated into the submission and the economic analyses as base case or scenario analyses.

B.3.13. Interpretation and conclusions of economic evidence

Based on the PAS price of isatuximab only (no discounts on comparators/subsequent therapies), the cost-effectiveness analysis estimates that IsaPd is associated with a QALY gain of 1.117 at an incremental cost of £184,947 resulting in an ICER of £165,554 when compared with Pd.

The base-case analysis has been conducted in line with the NICE reference case. The ICARIA-MM clinical trial provides mature OS, PFS, TTD data on IsaPd vs Pd as well as utility data in a 4th line population with RRMM that is generalisable to UK clinical practice.

The immaturity of the PFS and OS data, estimates of time on treatment, and patients who progress on 4th line therapy and the subsequent treatments received were identified as areas of uncertainty during the original Company submission. More mature OS, PFS and TTD data are now available from the ICARIA-MM trial providing more certainty to the model extrapolations, with 52.4 months of follow-up at the final OS data cut, compared with 11.6 months at the time of the original Company submission. 61.5% and 72.4% of patients had experienced an OS event and 67.3% and 86.2% had experienced a PFS event at end of follow-up in the IsaPd and Pd arm, respectively. Most patients had discontinued study treatment by the end of follow-up, with 15% of IsaPd patients and 3% of Pd patients remaining on treatment. Data from the SACT database was used to provide exploratory naïve comparative efficacy estimates against daratumumab monotherapy, validate trial PFS extrapolations, and to provide subsequent therapy costs from a real-word UK setting. Subsequent therapy adjustment analyses were explored to test the removal of the effect of subsequent treatment with daratumumab from both arms of the ICARIA-MM trial. The analyses conducted resulted in improved HR vs Pd, suggesting that the trial data used in the base case provided a conservative estimate of relative efficacy vs Pd.

Comparison of Pd outcomes from RWE with outcomes from the model suggest that the model may overestimate survival following treatment with Pd, and therefore comparative estimates of IsaPd vs Pd may be conservative. Median survival in MM-003, the pivotal Pd phase 3 study, was 13.1 months. Identified RWE studies reporting OS in Pd patients with three prior therapies reported median OS of 10.9 months and 9.7 months (45, 46, 263, 264). These are significantly lower than Pd survival seen in the ICARIA-MM trial and estimated from the model (median of 17.7 and 18.7 months, respectively).

An analysis vs daratumumab monotherapy is challenging given it was not possible to conduct an anchored comparison. In an exploratory analysis based on a naïve comparison of observational data (SACT), IsaPd is associated with a gain of [redacted] QALYs at an incremental cost of [redacted], leading to an ICER of £144,981 when compared with daratumumab. Any analysis vs daratumumab monotherapy needs to be interpreted with caution given the limitations outlined in Table 1 and the context in which IsaPd and daratumumab monotherapy are currently being used in clinical practice (i.e. in patients with different profiles).

Despite demonstrating improved PFS outcomes in the robust, placebo-controlled ICARIA-MM study as well as in NHS practice, this appraisal of IsaPd continues to highlight the inherent challenges in demonstrating cost-effectiveness of branded combination oncology products where the combination leads to better outcomes but is associated with longer treatment duration relative to comparators. Using the standard NICE reference case in the base-case analyses, we suspect that IsaPd will not be cost-effective even if isatuximab is priced at £0 (although actual discounts for other therapies are not known to Sanofi so cannot be included in our analysis).

IsaPd in this reappraisal has been disadvantaged by the loss of the EoL criteria (cost-effectiveness threshold of up to £50,000/QALY) due to the change in NICE methods and processes during the period in which IsaPd was accessible in the CDF. In contrast, both Pd and daratumumab monotherapy were previously accepted for use by NICE at the higher EoL threshold. If these therapies were to be assessed under the current reference case and methods, neither are likely to be a cost-effective use of NHS resources today. Therefore, Sanofi maintain that IsaPd should also be assessed at a WTP threshold of £50,000/QALY as was the expectation on entry into managed access and the case for the comparator treatments.

Non-reference-case analyses demonstrates the potential for IsaPd to be considered cost-effective. The current NICE guidance states that, in these circumstances, the committee may consider non-reference-case analysis with expensive or non-cost-effective background care costs removed. Therefore, analysis is presented removing the cost of likely non-cost-effective background care (Pd), where IsaPd is associated with an ICER of £43,344/QALY vs Pd (when only PAS for isatuximab was considered) and £61,407/QALY vs daratumumab monotherapy. When this was extended to include assumed discounts for other therapies and the [redacted], the ICER further decreases to [redacted] vs Pd and [redacted] vs daratumumab monotherapy. Cost-effectiveness will be further demonstrated at patent expiry of pomalidomide (expected Q2 2024). In an analysis that considered patent expiry

of pomalidomide (assuming a [redacted]) the ICER was [redacted] vs Pd and [redacted] vs daratumumab monotherapy. When relevant discounts are included and an [redacted] discount on isatuximab are incorporated, Sanofi anticipate that ICERs for IsaPd will be close to or below £50K/QALY vs Pd and daratumumab monotherapy [redacted] (Appendix Q). The future availability of IsaPd in a subcutaneous formulation will also further improve both the cost-effectiveness and reduce the budget impact of IsaPd. These analyses provide evidence that if the exceptionalities of this reappraisal are considered, routine commissioning of IsaPd can likely be considered a cost-effective use of NHS resources at £50,000/QALY and close to the £30,000/QALY threshold.

Applying value attribution to IsaPd further supports that the PAS price for isatuximab is value based. [redacted]. Clinicians expect that patients eligible for anti-CD38 treatments such as isatuximab will eventually decline due to earlier use of this treatment class but have indicated that there continues to be a need for IsaPd for 4th line patients now. [redacted], a recommendation for IsaPd is therefore, associated with a low budgetary impact and constitutes a short-term and low risk decision.

During its period in the Cancer Drugs Fund (CDF), IsaPd has represented an efficacious treatment option for the clinical community and more importantly for people living with multiple myeloma experiencing their 3rd relapse. The availability of daratumumab monotherapy and Pd, have not hindered CDF uptake of IsaPd, indicating that there is a continued medical need where clinicians choose IsaPd for appropriate patients at 4th line. Several treatments are expected to be licensed for these patients, meaning that outcomes will improve over time in patients who today receive IsaPd or other therapies at 4th line.

In an incurable cancer such as RRMM, continued access to IsaPd following the CDF period means that patients could maximise their time without progression, and remain alive to access further lines of therapy or enter clinical trials. We urge NICE and the committee to exercise flexibility in their decision making to ensure patients can continue to access a treatment that clearly fulfils an unmet need and is considered by clinical experts as the current SoC for 4th line RRMM patients.

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Appendices

The following appendices are provided in a standalone document:

Appendix C: Summary of product characteristics (SmPC) and public assessment report

Appendix D: Identification, selection, and synthesis of clinical evidence

Appendix E: Subgroup analyses

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality of life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: ICARIA-MM: ITT analysis

Appendix N: ICARIA-MM: 4th line subgroup additional analyses (supplementary to Document B)

Appendix O: SACT results by separate cohorts (CDF and EAMS)

Appendix P: Unanchored MAIC: IsaPd vs daratumumab monotherapy

Appendix Q: Cost-effectiveness analyses with estimated confidential comparator discounts

Appendix R: Survival analysis – diagnostic information

Appendix S: OS independent survival models

Appendix T: Non-reference case probabilistic sensitivity analysis results

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It's a plain English summary of their submission written for patients participating in the evaluation. It's not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it's sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

Section 1: submission summary

1a) Name of the medicine

Both generic and brand name.

Active ingredient: Isatuximab **Brand name:** SARCLISA®

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

The population being appraised by NICE Adults with relapsed and refractory multiple myeloma (RRMM) who have received at least two or more previous treatments, including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

On 30th May 2020, isatuximab received a marketing authorisation valid throughout the European Union (1). This authorisation was for isatuximab to be used in combination with pomalidomide and dexamethasone for the treatment of adults with relapsed and refractory multiple myeloma (RRMM) who have received at least two previous treatments (including lenalidomide and a proteasome inhibitor) and have demonstrated disease progression on the last therapy.

1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

The table below outlines our involvement with two patient advocacy organisations in the United Kingdom (UK) over the last 3 years.

2023

- **Cancer 52 -** Sanofi UK made a £10,000 contribution to the Cancer52 Corporate Supporters Programme but have no input into the programme content.

2022

- **Myeloma UK -** Sanofi UK was a pharmaceutical partner for the Myeloma UK London to Paris Bike Ride 2022. Sanofi UK donated £24,490 to support 10 Sanofi riders to participate in the bike ride, which aims to raise awareness of myeloma, and to raise funds to advance myeloma research.

- **Myeloma UK** – Myeloma UK chaired a workshop organised by Sanofi UK on combination therapies, and received £882 contribution. The aim of this workshop was to better understand the challenges around combination therapies and the views of relevant patient organisations.

2021

- **Myeloma UK -** Sanofi UK made a £19,000 contribution to Myeloma UK for the Identification of (monoclonal gammopathy of undetermined significance) MGUS Patients project but had no input into the content and/or materials. The aim of this project was to identify which patients are most likely to have received a diagnosis of MGUS from their primary care records and help identify predictors which could flag up MGUS patients that are at a higher risk of progression to myeloma (or the other clone-related complications).

- **Cancer 52** - Sanofi UK made a £10,000 contribution to the Cancer52 Corporate Supporters Programme but have no input into the programme content.

Section 2: current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Condition that the medicine treats

Multiple myeloma (MM) is a type of cancer that affects plasma cells (a type of white blood cell) in the bone marrow (2). Bone marrow is the soft, spongy centre of bone that produces many of the body's blood cells. Normally, plasma cells make antibodies that help you fight off infections. In MM, your plasma cells make antibodies which do not work properly, meaning your body cannot fight off infections as easily as before.

Relapsed MM occurs when the cancer comes back after a period of responding to treatment. When the cancer does not respond to treatment or gets worse despite treatment, it is known as refractory MM.

Almost half of patients diagnosed with MM will receive three or more different treatment regimens during their lifetime (3). However, with each additional treatment regimen, the length of response, quality of life, and survival are decreased (4, 5).

Approximately 5,900 people are diagnosed with MM every year in the UK, and approximately 17,600 people are living with MM in the UK at any one time (6). According to Cancer Research UK, 29% of patients survive MM for 10 or more years (7).

What is the impact of relapsed and refractory multiple myeloma on a person's quality of life?

Both relapsed and refractory multiple myeloma (RRMM) can have a significant impact on the quality of life of patients and their families/caregivers (8, 9). Patients may experience symptoms such as bone pain, fatigue, anaemia (where your body does not have enough red blood cells), and kidney problems, and may require frequent hospitalisation, chemotherapy, and other treatments, which can be physically and emotionally taxing (8, 9). The side-effects of treatment, such as nausea, vomiting, and nerve damage, can also affect a patient's quality of life. In addition, the uncertainty of the disease can cause anxiety and stress for both the patient and their loved ones.

Families and caregivers may also face challenges in caring for a loved one with RRMM. They may need to take time off from work or other responsibilities to provide care, which can impact their own quality of life. They may also experience emotional stress and worry about the patient's health and future.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How MM is diagnosed

MM is a complex cancer and its diagnosis can involve a number of different tests. Typically, diagnosis involves:

- Blood tests to look for high levels of certain proteins in the blood that can be used to diagnose MM
- Urine tests can also be used to detect certain proteins that may indicate MM
- Imaging studies such as X-rays, CT scans†, MRIs‡, or PET¶ scans may be used to look for bone damage or detect tumours in the bone marrow.
- Bone marrow biopsy (sample of bone marrow) may be taken from the hip bone or another large bone to look for cancer cells. Unlike the other tests, this may be a painful procedure.

Many of these tests are repeated regularly throughout all stages of treatment to measure response to treatment and monitor MM over time. Tracking the levels of normal and abnormal proteins in the blood via blood tests is particularly useful and is likely to be the most frequent test that patients will have.

Patients receiving isatuximab treatment should have blood tests before the first isatuximab infusion – these tests are typical for anti-CD38 drugs like isatuximab (which work by helping the immune system kill cancer cells).

†CT, computerised tomography; ‡ MRI, magnetic resonance imaging; ¶ PET, positron emission tomography.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

- Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.

The treatment pathway for MM in England is largely determined by recommendations made by the National Institute for Health and Care Excellence (NICE). A variety of combination treatments are available to patients, depending on the patient and their response to previous treatments (10). This means that patients receive different treatments, following each relapse.

The therapies available at 4th line are:

- Isatuximab, pomalidomide, and dexamethasone (IsaPd) in the CDF [TA648] (11)
- Pomalidomide and dexamethasone (Pd) [TA427] (12)
- Daratumumab monotherapy [TA783] (13)
- Ixazomib, lenalidomide, and dexamethasone (IxaRd) [TA870] (14).

Pd is a second-generation immunomodulatory medication and can be administered as an oral treatment. IxaRd is also an oral combination treatment, and although available as a 4th line treatment, it tends to be used more as a 3rd line therapy (15) and can only be used if a patient is not refractory to lenalidomide at 4th line. As lenalidomide is provided in earlier lines of therapy, at 4th line fewer patients now tend to receive therapies that include this drug. This highlights the need for varied treatment options at 4th line, allowing doctors to provide targeted therapies based on efficacy, but with tolerability, response to previous therapy, and patient preference considered.

Sanofi have spoken to UK doctors, who have noted that they generally prefer to treat patients with the treatment that delivers the best response and enables patients to live for longer without their disease progressing, but that frailer patients tend to receive daratumumab monotherapy at this line of therapy (16).

Isatuximab in combination with pomalidomide and dexamethasone (IsaPd) has been available to UK patients with 4th line RRMM since December 2019 as part of an Early Access to Medicines Scheme (EAMS), and on the National Health Service (NHS) via the Cancer Drugs Fund (CDF) since October 2020. Patients must have relapsed following their 3rd line therapy and have already received lenalidomide and proteasome inhibitor treatment.

This reappraisal considers longer-term data for IsaPd for the treatment of RRMM as a 4th line therapy. In the clinical trial that looked at the efficacy (how well a treatment works) and safety of IsaPd, ICARIA-MM (17-19), IsaPd provided a significant improvement in the length of time that patients can live without their disease progressing when compared with the trial comparator, Pd; median progression-free survival (PFS) increased by 5.85 months.

This shows the need for continued access to IsaPd as a treatment option after CDF funding to tackle the needs of patients requiring 4th line treatment. If reapproved by NICE, IsaPd will provide an additional treatment option for people living with MM and the clinical community.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

A patient preference study was conducted involving people living with MM in the UK and aimed to understand the relative importance they place on different features of treatment such as progression-free survival and treatment toxicity (20). Patients with MM were invited by the cancer charity Myeloma UK to participate in an online survey, and a total of 560 participants completed the survey (20). The study found that on average, most importance was placed on increase in progression-free survival, followed by severe or life-threatening toxicity, and mild or moderate chronic toxicity (20). They found that those who gave more importance to severe or life-threatening toxicity over mild or moderate chronic toxicity (56% of patients) tended to be younger (≤70 years old), were working, and looking after dependent family members (20). These patients also experienced severe or life-threatening side effects more frequently (20).

A survey was also undertaken by Sanofi in 2022 (not published) to understand the values and preferences patients place on different treatments and to evaluate the relative importance of factors affecting treatment choice. The survey included 91 adults aged 18 years+ in England, Scotland, and Wales who had been diagnosed with MM for a minimum of 3 months and were currently receiving their first, second, or third treatment (survey conducted between 21 April 2022 and 18 June 2022). When asked about their desired outcome from treatment, 75% said “to prevent my cancer coming back for as long as possible”, and 70% said “to help me live longer”. The majority (75%) of patients felt that being involved in decisions about to their treatment was important and were at least somewhat involved – primarily discussing and making the decision together with their health-care provider. Of note, only 11% of patients said that intravenous (IV) administration would prevent them from selecting a treatment; severity of side effects and time that disease was under control were seen as more important considerations when choosing between treatment options.

Independent statements provided by a patient during the consultation for the initial NICE appraisal for IsaPd highlighted the physical and psychological burden that patients and their carers experience, especially after a third relapse, where treatment options become limited. They also noted the reassurance of knowing

that ‘they have access to the best possible treatment to give them a few more months/years of life’ (11).

It is important to note that treatment preferences are varied and unique to each individual and their situation, however the existing patient-based evidence suggests that keeping the disease under control is of key importance to patients.

Section 3: the treatment

3a) How does the new treatment work? What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Isatuximab works by attaching to a protein called CD38 that is present on the surface of myeloma cells. This highlights the cell to the immune system (the body’s natural defences), allowing the immune system to target and kill the myeloma cells (1).

A summary of the products characteristics is available at the following link: https://www.ema.europa.eu/en/documents/product-information/sarclisa-epar-product-information_en.pdf

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

☒Yes

☐No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Isatuximab is used in combination with pomalidomide and dexamethasone for patients with RRMM who have received at least two or more previous treatments, including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy.

Pomalidomide is a targeted cancer drug and works in a number of ways, including:

- Stopping the myeloma cells developing
- Stopping blood vessel growth that helps cancer cells grow and survive
- Encouraging the immune system to kill the myeloma cells

Common side effects of pomalidomide include anaemia (low red blood cell counts), neutropenia (low white blood cell count), tiredness, thrombocytopenia (low platelet counts), fever, peripheral oedema (swelling of the limbs due to fluid retention), peripheral neuropathy (nerve damage causing tingling, pain and numbness in the hands and feet) and infections including pneumonia (infection of the lungs) (21).

Dexamethasone is a steroid. It helps pomalidomide to work better and to kill myeloma cells.

Common side effects of dexamethasone include hyperglycaemia (high blood sugar levels), insomnia (difficulty sleeping), muscle pain and weakness, asthenia (weakness), tiredness, oedema (swelling) and weight gain (22).

By taking pomalidomide and dexamethasone alongside isatuximab, the treatment covers different complementary mechanism of action to target myeloma disease.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Isatuximab

10 mg/kg intravenous infusion (IV), on days 1, 8, 15, and 22 of the first cycle, then every 2 weeks for the second cycle and beyond (days 1, 15). Each treatment cycle consists of a 28-day period and is repeated until disease progression or unacceptable toxicity.

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 IV, on days 1, 8, 15 and 22 of each 28-day cycle. Dexamethasone should be administered only once before isatuximab IV infusion, as part of the backbone treatment and premedication (alongside the other recommended medicinal products) to reduce the risk and severity of infusion reactions (IRs).

The treatments are usually given until disease worsens but treatment may be ended if patients experience unacceptable side effects.

The isatuximab component of the combination treatment is delivered by a healthcare professional, in an appropriate environment. This may affect patients and carers as the number of visits to the clinic/hospital will increase compared with other therapies available at 4th line which are primarily oral (tablets) or provided as an injection.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The clinical efficacy (how well IsaPd works) and safety of IsaPd has been studied in one main study, ICARIA-MM (NCT02990338). ICARIA-MM looked primarily at how IsaPd prolonged a person's progression-free survival, compared with people who had been randomly allocated to receive Pd only instead (18, 19, 23).

People who could participate in ICARIA-MM were adults aged 18 years or older, who had received at least two previous treatments and who had not responded to lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib, or ixazomib), and whose disease had progressed on or within 60 days after the end of their last treatment. The study enrolled 307 participants with RRMM across 96 centres in 24 countries. Of these, 110 participants with RRMM had received three prior lines of treatment (4th line).

Additional data were available from the systemic anti-cancer therapy (SACT) dataset (24). This dataset collects information on the usage of cancer therapies from NHS England providers. It allows us to understand treatment patterns, how long patients receive certain treatments and how long they live with a cancer. Data were collected between December 2019 and March 2022 from 24 centres across England, including 737 people with RRMM treated with only IsaPd in the NHS.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results?

Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The ICARIA-MM study included 307 people with RRMM that had not improved with previous treatments, and showed that adding isatuximab to pomalidomide and dexamethasone can delay the disease progressing or worsening (18, 19, 23).

Of these, 110 participants were receiving 4th line treatment. In these participants, those receiving IsaPd lived for 12.4 months (95% CI 7.4, 27.7) without their disease getting worse (an outcome known as progression-free survival ([PFS]) compared with 6.5 months (95% CI 4.5, 10.1) for participants receiving Pd (18, 19, 23). Notably clinicians opt to use the treatment which offers the longest period of PFS (16), and this outcome is highly valued by patients who are facing their 3rd relapse (20).

Furthermore, with a median follow-up ~4 years, the average overall survival (OS, the total length of time that patients lived following the start of treatment), was 33.28 months (95% CI: 18.431, 54.275) in the IsaPd arm and 17.71 months (95% CI: 11.565, 27.532) in the Pd arm (1, 23). This represented a clinically-meaningful improvement in survival compared with Pd alone (18, 19, 23).

In the ICARIA-MM trial, there were some differences seen in the treatments that patients received after their disease worsened compared with the treatment options people living with MM would have access to in the UK. This is mainly due to the multinational nature of the clinical trial which means that patients in other countries are able to use different treatments, some of which may not be available in the UK. In the Pd arm of the ICARIA-MM trial, more people received daratumumab-based therapies as subsequent treatment. These would not be accessible in the UK because daratumumab is only available at 4th line in the UK. This difference could affect the estimate of how well a treatment improves survival compared with other treatments.

In the SACT analysis, data was available for 737 patients. Patients in the SACT analysis tended to be slightly older, there were more males, and were less fit compared with patients treated with IsaPd in the ICARIA-MM trial (1, 23, 24). The average OS in the SACT dataset was 18.8 months (95% CI: 15.7, 22.9) (572 days) with a median follow-up for OS of 9.4 months (24). Additionally, the median time a patient was treated with IsaPd was 8.9 months (95% CI: 7.3, 10.8) (270 days),

which is comparable to the treatment duration seen in 4th line population of the ICARIA-MM trial. The length of time that patients were followed-up was short in the SACT dataset compared with the ICARIA-MM trial and over half of the patients were still alive at the time the most recent data was reported.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Treatment-related toxicities, especially in the context of multi-drug regimens, can impact patients' quality of life (QoL). The available data indicate that this is not the case when isatuximab is added to pomalidomide and dexamethasone. In the ICARIA-MM trial, the addition of isatuximab to pomalidomide and dexamethasone did not have a negative impact on patients' QoL. During the trial, QoL did not change significantly from baseline (before treatment started).

In addition to this, a patient preference study involving 560 patients who were recruited via Myeloma UK, reported that the majority of participants considered increasing the probability of being progression-free for 1 year or longer to be more important than simultaneously decreasing the chance of experiencing severe or life-threatening toxicity or experiencing mild or moderate chronic toxicity, suggesting that patients are willing to experience some side-effects if the treatment can achieving longer term survival without disease progression (20).

QoL was measured in the trial using three different questionnaire-based tools (the EORTC-QLQ-C30, the QLQ-MY20 and the EQ-5D-5L) (25). The tools assessed key themes including disease symptoms, pain and fatigue, physical functioning (the ability to perform usual daily tasks), role function (the ability of an individual to perform tasks typical of their age and responsibility) and overall health status/quality of life. All these assessments showed the same trend; patients receiving IsaPd treatment maintained a stable QoL (25).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will

support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Based on data from the ICARIA-MM trial, the most common side-effects with IsaPd (which may affect more than 1 in 5 people) are neutropenia (low levels of neutrophils, a type of white blood cell), infusion reactions, pneumonia (infection of the lungs), upper respiratory tract infection (such as nose and throat infections), diarrhoea, and bronchitis (inflammation of the airways in the lungs) (26).

The most common serious side-effects with IsaPd are pneumonia and neutropenia. The doctors and nurses managing treatment will closely monitor patients for response and side effects, and in some cases, treatment may be delayed or may be discontinued if the side-effect requires hospitalisation, or is life threatening (26).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

MM is incurable and is characterised by periods of relapse and remission. The period spent without the disease worsening tends to decrease with each relapse. This amount of time before MM relapses (progression-free survival; PFS), is the primary treatment goal in MM and treatments that lengthen this time are extremely important (27).

IsaPd is a triplet regimen (combining three different medicines) where an anti-CD38 antibody (isatuximab) is given alongside an immunomodulatory drug (IMiD, pomalidomide) and a steroid (dexamethasone) (16). Combination therapies such as IsaPd bring several medicines together to attack cancer cells in different ways (28). This can make them more effective in treating the cancerous cells, including those cells that have developed resistance or stopped responding to existing drugs (29). Clinical opinion has indicated that a triplet regimen becomes more important as a treatment option at 4th line because patients tend to have relapsed several times and have already stopped responding to other treatments (16).

The ICARIA-MM trial showed that adding isatuximab to pomalidomide and dexamethasone can delay worsening of the disease compared to receiving Pd only (23). Other trials have shown that triplet regimens are better than doublet regimens in terms of response rate and PFS in RRMM (30). The response rate

with IsaPd is higher and the duration of response is longer than seen for alternatives (Pd and daratumumab), and patients typically remain on IsaPd longer than on Pd and daratumumab, although IsaPd has not been directly compared with daratumumab in a clinical trial (16, 18, 23).

Since the IsaPd combination was made available through EMAS and the CDF for patients with 4th line RRMM, more than 700 people living with MM have been able to receive this therapy. This highlights the need for the continued availability of this medicine (24).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

While IsaPd has the potential to address an unmet need amongst patients at 4th line, those receiving treatment with IsaPd will need to attend the hospital to receive isatuximab as an IV infusion. This would require more hospital visits compared with current treatments which are delivered as a tablet (Pd) or via an injection (daratumumab monotherapy) and can mean time out of work or daily activities to attend hospital appointments and may place additional burden on patients and carers.

Patient preference data shows that patients place more value on the time that their disease is controlled compared with other treatment features. Consistent with published data (18, 23), advice from clinicians indicated that the more patients respond to treatment, and for longer with IsaPd than alternative treatments (Pd and daratumumab). Patients also typically remain on IsaPd longer than on Pd and daratumumab i.e. they benefit from longer periods without disease progression with IsaPd (16). In addition, clinicians indicated that a good effective treatment with fewer toxicity issues (16) relative to alternatives, offsets the mode of delivery. As such, they did not consider the IV administration to prohibit the use of IsaPd at 4th line, given the favourable efficacy and toxicity profile (18, 23).

Indeed, high uptake of IsaPd in the SACT data (>700 patients accessing treatment) shows that despite the commitment for hospital visits, people living with MM value IsaPd as a treatment option at 4th line.

As with all treatments there can be side-effects (listed in Section 3g). However, clinical trials evidence indicate that IsaPd has a manageable safety profile.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?

- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

The chosen model has been used in previous appraisals within MM. Its structure is known as the 'partitioned survival' approach, with patients able to be in health states that are relevant to MM:

- Progression-free (on-treatment or off-treatment)
- Post-progression (on-treatment or off-treatment)
- Death.

At the start of the model, all patients are in the progression-free state and on treatment. However, over time the disease can worsen (some patients may relapse) and they move to the post-progression state where they receive further lines of therapy for their disease, or they may die at any point during their treatment journey.

The percentage of patients in each health state is defined by three curves representing the following:

- Overall survival curve – the percentage of patients alive
- Progression-free survival curve – the percentage of patients alive without disease progression
    - The difference between the overall survival and progression-free survival curves – the percentage of patients whose disease has progressed and may be receiving other therapies.
- Time to discontinuation curve – the percentage of patients on treatment.

Modelling how treatment extends life

Treatments extend life by slowing disease progression. The trial followed patients for over 4 years, however, some patients in the clinical trial are still on treatment with IsaPd or another subsequent treatment and are alive. Therefore, most recently available data from the trial needed to be extrapolated for a patient's lifetime.

Modelling how much a treatment improves quality of life

The model assigns values (called utility values) to progression-free and post-progression health states to represent a patient's QoL. These values, between 0 and 1 (0 representing death to 1 representing perfect health), indicate how patients feel about their overall health at each phase of their treatment journey. These values came from data collected during the ICARIA-MM trial for patients that received IsaPd or Pd.

As patients in the progression-free state have a better QoL than patients in the progressed disease state, by slowing disease progression, those treated with IsaPd have a better overall QoL.

Modelling how the costs of treatment differ with the new treatment

IsaPd is associated with an increase in costs for the NHS compared with current treatments. This is mainly due to the addition of isatuximab onto an already established combination treatment, Pd. Due to the IV administration of isatuximab, there will also be additional costs for the NHS compared to current standard-of-care therapies, such as those administered orally. These have been accounted for in the economic model.

Uncertainty

As not all patients were followed up until death in the ICARIA-MM trial, long-term predictions of overall survival, progression-free survival, and time to discontinuation for IsaPd and Pd have been estimated beyond the trial follow-up period (i.e. extrapolated). These predictions are uncertain and as a result, different predictions have been considered and tested.

Another source of uncertainty are the outcomes for the comparison with daratumumab monotherapy. There are no clinical studies that directly compared IsaPd and daratumumab monotherapy in the same study. Instead, data from the SACT dataset in England (examining use of IsaPd and daratumumab monotherapy in clinical practice) has been used to inform the effectiveness of both these treatments in the economic model. However, only few information about the patients that received treatment (e.g., age, performance status) were available from SACT. Clinicians have also advised that whilst daratumumab monotherapy was available in the CDF, the treatments available after patients progressed is different to what patients have currently available after IsaPd. These features of this data means that it is difficult to draw reliable conclusions about the long-term outcomes such as overall survival when comparing these treatments.

Cost-effectiveness results

When using the discounted price of isatuximab only and non-discounted price for all other treatments, the economic analysis shows that there is an incremental

cost-effectiveness ratio (ICER†, representing incremental cost per quality-adjusted life year [QALY]†) of £165,554 when IsaPd is compared with Pd. When IsaPd is compared with daratumumab monotherapy, the ICER is £144,981.

The true cost-effectiveness of IsaPd is not known because there are agreed discounts available to the NHS for comparators and other treatments used in the economic model. These discounts are not known to Sanofi. However, the NICE committee will be able to consider the cost-effectiveness results with confidential discounts applied in their deliberations.

Additional factors

There are currently no agreed ways of assessing cost-effectiveness of medicines that are used in combination such as IsaPd, where isatuximab is added to an existing backbone therapy, Pd. The addition of isatuximab to Pd increases the PFS and whilst this is important for patients, for the health system this increases the total cost of the treatment as the time where both treatments are used together increases. Sanofi are only able to modify the price of isatuximab within the IsaPd combination (it is not the manufacturer of pomalidomide, or dexamethasone) and so it is difficult to show that combination treatment as a whole is cost-effectiveness.

†Refer to glossary

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

There remains a significant unmet need for patients with RRMM at the 4th line of treatment, with currently available options having poor overall and progression-free survival. As demonstrated by the ICARIA-MM trial, adding isatuximab to pomalidomide and dexamethasone can delay progression of the disease. As stated in earlier sections, clinical opinion has also indicated that there is no other treatment available at 4th line that is as effective as IsaPd (16).

MM is incurable and is characterised by periods of relapse and remission, and the period spent in remission (progression-free) tends to decrease with each successive relapse (27). The amount of time before MM relapses (PFS), is the primary treatment goal in MM. Clinicians have also noted that it is better for patients to have the treatment that gives the longest PFS in order to minimise MM-associated damage to other organs (e.g. bone disease, renal issues) (16). The ICARIA-MM trial has demonstrated that there is a 46.4% reduction in risk of disease progression or death for IsaPd compared with Pd (18, 19, 23).

Independent statements provided by a patient during the initial NICE appraisal for IsaPd highlighted the physical and psychological burden they and their carers experience, especially after a third relapse, where treatment options become

limited. They highlight the worry for future and the impact of their disease and possible death on their loved ones (11). People living with MM do not want to feel abandoned, especially when they have experienced several relapses, and at which point additional time spent in remission/progression free becomes incredibly important to patients and carers alike.

Continued access to IsaPd at 4th line provides a longer time before the disease relapses and so can provide hope for more effective treatments to become available for when patients eventually relapse.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

In 2022, NICE changed the way in which treatments are appraised. Specifically, replacement of the end-of-life (EoL) modifier (which applied in the original appraisal) with the new severity modifiers may disadvantage older patients and those approaching EoL (31, 32). Because NICE appraisals for Pd and daratumumab monotherapy were concluded before the new NICE manual was published, they were not assessed under the new methods. This means that IsaPd is now assessed under a different framework compared to other treatments available at this line of therapy.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

- ICARIA-MM – Study comparing isatuximab, pomalidomide, and dexamethasone to pomalidomide and dexamethasone in refractory or relapsed and refractory multiple myeloma patients. Available at: https://clinicaltrials.gov/ct2/show/NCT02990338
- Myeloma UK isatuximab treatment guide. Available at: https://www.myeloma.org.uk/wp-content/uploads/2022/11/Myeloma-UK-Isatuximab-Treatment-Guide.pdf

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Confidence interval (CI): A range of values that you can be 95% certain contains the true mean of the population.

Clinical trial/clinical study: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease.

Incremental cost-effectiveness ratio (ICER): The ICER is the difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest.

NICE: The National Institute for Health and Care Excellence. An independent organisation set up by the government to decide which drugs and treatments are available on the NHS in England.

Quality of life: A measure of the overall enjoyment and happiness of life including aspects of an individual's sense of well-being and ability to carry out activities of daily living.

Quality adjusted life years (QALYs): QALYs are an overall measure of health outcome that weight the life expectancy of a patient with an estimate of their HRQoL (measured on a 0–1 scale).

Standard-of-care: Treatment that is accepted and widely used by medical experts and healthcare professionals for a certain type of disease.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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12. National Institute for Health Care Excellence (NICE). Single Technology Appraisal: Pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib (review of TA338) (TA427). Committee Papers. Available at: https://www.nice.org.uk/guidance/ta427/documents/committee-papers (last accessed March 2023). London: National Institute for Health and Care Excellence; 2016 23 November.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [Review of TA658] [ID4067]

Additional evidence: SACT data for pomalidomide

November 2023

File name	Version	Contains confidential information	Date
ID4067-IsaPd-RRMM_Additional evidence SACT data for pomalidomide-Redacted.docx	1.0	No - Redacted	30 November 2023

Table of contents

Executive summary

Since the company submission for isatuximab in combination with pomalidomide and dexamethasone (IsaPd) was made in April 2023, real world evidence from the SACT database for the primary comparator Pd has become available. We believe this information is highly relevant to the appraisal. As agreed with NICE, this addendum therefore includes the following:

- A summary of the real world evidence study
- A naïve comparison of Pd SACT and IsaPd SACT
- An updated cost-effectiveness analysis and revised base case utilising this data.

Sanofi recently conducted a retrospective study using the National Cancer Registration and Analysis Service (NCRAS) Cancer Analysis System (CAS) database to describe, among patients diagnosed with MM, the real-world patient demographic and clinical characteristics, treatment patterns, clinical outcomes, and healthcare resource use. Although this study was conducted to understand newly diagnosed MM patients in England, RWE from diagnosis to death/loss to follow-up was captured, and as a result, data relating to pomalidomide use in later lines was also available.

Recent feedback to the company from three myeloma clinicians continues to support that the relevant comparator to IsaPd in the 4th line population is Pd. They note that since the introduction of IsaPd into the pathway via the Cancer Drugs Fund (CDF), only a minority of UK patients (those who are pancytopenic or are otherwise unfit/contraindicated for therapy with IsaPd or due to patient choice) will be prescribed daratumumab monotherapy at 4th line. Therefore, the focus of the addendum and evidence presented is the comparison vs Pd.

In the company submission, the primary evidence for Pd was derived from the ICARIA-MM trial. This evidence is confounded by the use of post-study treatments that are not available in the UK. At the time of the submission, SACT data was available for IsaPd and daratumumab monotherapy (DARA) but was not available for Pd. Whilst only a naïve comparison of IsaPd SACT and Pd SACT is feasible, given that the baseline characteristics available are comparable, the data was collected from the same database and that this reflects English clinical practice, this analysis likely reflects the most suitable evidence for decision making. Indeed, in previous NICE appraisal of CDF treatments, data from SACT have been accepted and used as critical evidence to inform the decision making. Notably, the committee appraising daratumumab DARA in RRMM [TA783] had expressed preference for utilising real-world data from the SACT database and highlighted the value of this data to inform future appraisals (1).

The revised economic analysis using the IsaPd and Pd SACT data demonstrates that the cost effectiveness of IsaPd vs Pd can be improved when real-world outcomes of treatment are considered.

As previously outlined in the submission, there are several challenges facing this appraisal including the loss of the end-of-life (EoL) criteria and the difficulty in demonstrating cost-

effectiveness for a branded triplet combination therapy. Sanofi maintain that the EoL threshold should be retained for the assessment of IsaPd, but nevertheless testing applicability of a severity modifier using the data from Pd SACT demonstrated that the 1.2 modifier would apply.

Given the unique challenges disadvantaging this appraisal, as per the April 2023 submission, non-reference case analyses are also provided.

Sanofi urge the appraisal committee to take a pragmatic approach and exert flexibility in their decision-making to ensure that patients are not inadvertently disadvantaged by the complex issues surrounding this appraisal and are able to continue accessing this effective combination therapy outside of the CDF.

1 Sanofi NCRAS study- RW evidence on pomalidomide at 4th line of therapy

Until now, the evidence for Pd was derived from the 4th line subgroup of the ICARIA-MM trial, whereas data for IsaPd and DARA were available from SACT. To address the gap in real-world data for Pd from SACT at 4th line therapy comparable to IsaPd SACT data available from NHS Digital, the company submits additional evidence from a retrospective study using SACT data. The data presented in this addendum collected via SACT represents the most recent source of real-world evidence for Pd in England (outcomes data available until Aug 2021). The broad study objectives and the derivation of data relevant to this appraisal have been set out within the addendum in **Error! Reference source not found.**.

1.1 Methods

1.1.1 Research questions and objectives

The detailed objectives of the primary study are provided in **Error! Reference source not found.**. In summary, the objectives of the primary study were to describe (overall, by line of therapy (LoT) [i.e. 1st line, 2nd line, 3rd line, 4th line], and transplant status, as necessary):

1. The patient demographic and clinical characteristics at MM diagnosis and, where available, at the initiation of each LoT.

2. The treatment pathway and patterns for patients with newly diagnosed MM.

3. The distribution of SACT treatments (mono/combo regimen level) received after MM diagnosis among patients with at least one SACT record.

4. The longitudinal sequencing of SACT treatments (1st line to 4th line) received among patients with MM and at least one SACT record.

5. The duration of treatment for patients with MM and at least one SACT record.

6. Treatment outcomes (PFS and OS).

7. HCRU outcomes from diagnosis until death or loss to follow-up among patients with MM and at least one SACT record.

The data presented in this addendum describes the following among 4th line patients;

1. Demographic and clinical characteristics of patients at initiation of any 4th line treatment.

2. Treatment duration and time to next treatment (TTNT) on pomalidomide.

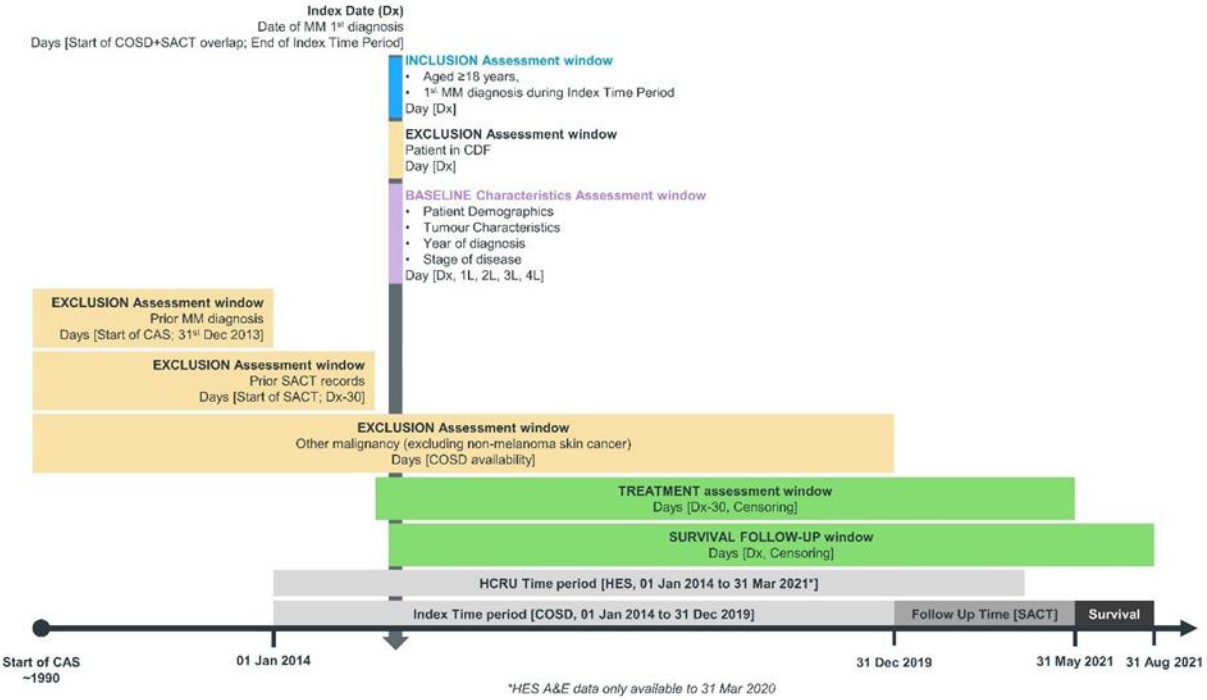
3. Treatment outcomes on pomalidomide (time to next treatment or death [TTNTD] and overall survival [OS]).

1.1.2 Study design

The primary study design, localised for the 4th line population, is described below. The detailed methods and results of the primary study are provided in **Error! Reference source not found.**.

This was a descriptive, non-interventional, retrospective population-based cohort study to identify patients in England newly diagnosed with MM, and to understand their characteristics, treatment patterns, clinical outcomes, and health care resource use (HCRU). Study participants were identified from the Cancer Analysis System (CAS) database and their records linked to the Hospital Episode Statistics (HES) database. An overview of the study design and study time period are provided in Figure 1. The overall study time period was from 1 January 2014 to 31 August 2021, with slight variations in the periods with available data for patient identification, treatment pathway, and survival ascertainment.

Figure 1: Study design diagram



Abbreviations: A&E, Accident & Emergency; CAS, Cancer Analysis System; CDF, Cancer Drug Fund; COSD, Cancer Outcomes and Services Dataset; Dx, diagnosis; HES, Hospital Episode Statistics; MM, multiple myeloma; nL, nth line of therapy; SACT, Systemic Anti-Cancer Treatment.

1.1.3 Population coverage

All adult patients newly diagnosed with MM during the patient identification time period were considered for inclusion in the study. Diagnoses of MM were identified using the 10th version of International Classification of Diseases (ICD-10) code: C90.00.

1.1.3.1 *Inclusion criteria*

Patients were eligible for inclusion in the study cohort if they met all the following criteria:

- Incident diagnosis of MM

- Aged ≥18 years at the date of incident MM diagnosis.

1.1.3.2 *Exclusion criteria*

Patients were excluded from the study cohort if they met any of the following criteria:

- A record of SACT more than 30 days prior to the date of incident MM diagnosis.
- A record of MM diagnosis prior to the Patient Identification Time Period.
- A record of any other malignancy within the Study Time Period, except for non-melanoma skin cancer.

1.1.3.3 *Study cohorts*

A summary and description of all study cohorts are provided in Table 1.

Table 1: Description of study cohorts

Cohort	Description
Overall cohort	All eligible patients with MM, excluding patients who had received (at any LoT) a drug which was on the CDF list at the time of analysis
SACT-treated cohort	All eligible patients with MM who received at least one SACT, excluding patients who had received (at any LoT) a drug which was on the CDF list at the time of analysis
CDF cohort	All eligible patients with MM who had received (at any LoT) a drug which was on the CDF list at the time of analysis, as agreed with NHS Digital.

Abbreviations: CDF, Cancer Drugs Fund; LoT, line of treatment; MM, multiple myeloma; SACT, Systemic Anti-cancer Therapy.

1.1.4 Data sources

NHS Digital collects, stores, and analyses data through the National Disease Registration Service (NDRS). An important component of NDRS is the National Cancer Registration and Analysis Service (NCRAS), which maintains the datasets that comprises CAS. A summary and description of the data sources, as well as the linking used between them, informing this study are provided in **Error! Reference source not found.**.

1.1.4.1 *Exclusion of CDF-funded therapies*

Outcomes data for patients who had received (at any LoT) a drug that was on the CDF list at the time of study data extraction are excluded by default from the analysis to avoid compromising the National Institute for Health and Care Excellence (NICE) appraisal process and managed access arrangements. Patients who received any therapy from the CDF list at the time of analysis were included in demographic and clinical descriptions only as an exploratory objective, however these data are not relevant to the decision problem and hence are not presented here. The therapies on the CDF register as of 24 March 2022 when the study was executed, are listed in Table 2.

IsaPd SACT data provided directly by NHS Digital to the company and the SACT data for daratumumab monotherapy available from the TA783 committee papers were already presented as part of the company submission.

Table 2: Treatments for MM on the CDF register at the time of study data extraction and excluded from the analysis

Blueteq reference	Drug
DAR2_v1.5	Daratumumab + bortezomib + dexamethasone for 2nd line. For 3rd line, if 2nd line consisted of ixazomib + lenalidomide + dexamethasone
ISA1_v1.1	Isatuximab + pomalidomide + dexamethasone for 4th line
IXA1_v1.5	Ixazomib + lenalidomide + dexamethasone for 3rd line/4th line

Abbreviations: CDF, Cancer Drugs Fund; MM, multiple myeloma.

1.1.5 Data collection

1.1.5.1 *Variables*

Table 3 provides a summary of all patient populations of interest, index dates, variables to be reported, and stratifications required for each study objective relevant to the decision problem. Patients receiving drugs through the CDF at the time of study execution are excluded from all patient populations unless otherwise specified.

Table 3: Summary of variables relevant to the decision problem reported by study objective

Objective	Population	Index Date	Variables	Stratification (1)	Stratification (2)
1. Demographic and clinical characteristics	All patients with MM	Start of LoT	Age Weight ECOG score Follow-up time	None (overall)	-
5. Duration of treatment	SACT-treated patients	Start of LoT	TD TTNT	LoT	SACT regimen groups
6. Survival outcomes	SACT-treated patients	Start of LoT	PFS (proxied by TTNTD) OS	LoT	SACT regimen groups by top 5 most common

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LoT, line of treatment; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival; SACT, systemic anti-cancer therapy; TD, treatment duration; TTNT, time to next treatment; TTNTD, time to next treatment or death.

Baseline variables

Patient demographic and clinical characteristics were captured from the relevant database for each variable (CAS [Cancer Outcomes and Services Dataset (COSD) and SACT] and HES) and reported for all eligible patients, for the overall cohort (i.e., all eligible patients excluding CDF), for the SACT-treated cohort, and for the CDF cohort.

At 4th line treatment initiation, only the following baseline characteristics were available:

- Weight
- Age
- ECOG
- Follow-up time from start of 4th line.

These data were not collected per treatment regimen and by LoT from the study conducted. A description of the full cohort of newly diagnosed MM patients with additional characteristics available are presented in **Error! Reference source not found.** for information.

Outcome variables

Available follow-up time was defined as the maximum time a participant could contribute to the planned analyses across the study period. Outcomes were captured from COSD, SACT, and HES linked databases and described for patients in the SACT-treated cohort reaching each LoT (Table 4 and Table 5).

Treatment duration was defined as the time from the start date of a LoT to the earliest of the end date of a LoT/regimen or date of death (reported using Kaplan-Meier approach). Treatment duration outcome available from IsaPd SACT data provided by NHS Digital uses similar methods to define this endpoint. The detailed methods for identifying the end of a LoT and regimen end dates for this retrospective study have been described in **Error! Reference source not found.**.

Time to next treatment (TTNT) was defined as the time from the start date of each LoT (1st line - 4th line) to the start date of the next LoT. These data are not discussed at length in this addendum as they tend to over or underestimate the real PFS duration for patients that receive a given therapy but are provided for context.

In the study, time to next treatment or death (TTNTD) was used as a proxy for rwPFS as it aligned closely to the International Myeloma Working Group (IMWG) rationale for advancement of a line of therapy (a new LoT begins when a planned treatment programme is modified to include additional agents [alone or in combination] as a result of disease progression, relapse, or toxicity, or when a planned treatment break is interrupted by a need for additional treatment (2)). However, this data was not available from the other SACT sources used to inform the current decision problem.

OS was measured as the time from the start of each line of therapy until the date of death from any cause.

Both OS and rwPFS measures were reported using Kaplan-Meier analysis from the initiation of each LoT, overall and stratified by SACT regimen group. Both outcomes were anchored to start measuring survival time from the start of LoT of interest, among those patients who had the respective number of LoTs observed during follow-up. The number of patients contributing to each analysis are reported. As with all SACT analyses, individual patient level

data are not available and only aggregate data are made available based on the pre-specified objective and research question.

Table 4: Variables describing Treatment duration, TTNTD and OS

Variable	Operational definition	Data source(s)
Treatment duration	Number of months from the LoT initiation until the LoT end date	SACT
Time to next treatment or death	Number of months from LoT initiation until the earliest date of next LoT initiation or death from any cause	COSD, HES
Overall survival	Number of months from LoT initiation until the date of death from any cause	COSD, SACT, HES

Abbreviations: COSD, Cancer Outcomes and Services Dataset; HES, Hospital Episode Statistics; LoT, line of treatment; SACT, Systemic Anti-Cancer Therapy; TTNTD, time to next treatment or death.

Table 5: Points of interest for Treatment duration, TTNTD and OS outcomes

Variable	Treatment duration	Time to next treatment or death	Overall survival
Index date	Start of 1st line, 2nd line, 3rd line, 4th line	Start of 1st line, 2nd line, 3rd line, 4th line	Start of 1st line, 2nd line, 3rd line, 4th line
Event (end date)	Earliest of: • End date of current LoT/ regimen • Date of death	Earliest of: ▪ Date of start of next LoT (TTNT) ▪ Date of death from any cause	Date of death
Censoring (end date)	Earliest of: • End of treatment pathway time period (31 May 2021) • Date of loss to follow-up	Earliest of: ▪ Date of loss to follow-up ▪ End of treatment pathway time period (31-May-2021)	Earliest of: ▪ End of survival ascertainment time period (31-Aug-2021) ▪ Date of loss to follow-up ▪ Date of last vital status for patients determined "alive"†

Abbreviations: LoT, line of treatment; TTNTD, time to next treatment or death; OS, Overall survival
†Vital status can be alive, unknown, or dead. If dead, the specific death date is used.

1.1.5.2 *Line of therapy algorithm*

The International Myeloma Working Group (IMWG) defines a LoT as one or more cycles of a planned treatment programme (2). This might consist of one or more planned cycles of a single-agent or combination therapy, or a sequence of treatments administered in a planned manner (e.g. induction therapy, consolidation therapy, SCT procedure, and maintenance therapy). A new LoT begins when a planned treatment programme is modified to include additional agents (alone or in combination) as a result of disease progression, relapse, or toxicity, or when a planned treatment break is interrupted by a need for additional treatment.

Since LoTs are not directly recorded or defined in CAS, for each patient, SACT agents and regimens were combined into LoTs using a novel, devised algorithm based on the IMWG criteria. Available treatment guidelines and collaboration and validation from a MM clinical

expert were also utilised to ensure that the algorithm was able to reflect clinical practice with regimens of interest.

Rules for identifying each LoT

Generally, the following rules were applied for identifying each LoT (Figure 2):

[redacted]

Figure 2: Diagram illustrating steps a) to d) of the LoT algorithm

[redacted]

Abbreviations: LoT, line of treatment; SACT, systemic anti-cancer therapy.

Additional rules were applied to incorporate LoTs including stem cell transplants at earlier lines of therapy (**Error! Reference source not found.**, Section A.1.6.1 and A.1.6.2).

Regimen end dates

End dates of SACT regimens or cycles are not recorded in CAS. Therefore, regimen end date was calculated as the start date of the latest cycle within the regimen + the median cycle duration for the corresponding SACT regimen (BENCHMARK_GROUP) per patient. To avoid excessive cycle lengths, the median cycle length will be limited to a maximum length as per guideline for each regimen + allowable grace period of seven days. See **Error! Reference source not found.**, Section A.1.6.3, Table 26 for cycle duration per regimen as per guidelines.

During the COVID-19 pandemic, multiple cycles may have been prescribed at the same time. Duration of cycle was therefore defined as number of cycles (with differing cycle IDs) with the same cycle start date (same SACT agents) multiplied by median duration of cycle. To avoid excessive treatment duration calculations, number of cycles starting on the same day will be capped at three.

SACT regimens containing supportive agents only (e.g., denosumab) will be ignored during patients' treatment sequencing. For combination SACT regimens containing both supportive and SACT agents, the supportive agent will be ignored and only the SACT agents of the regimen will be presented within a patient's treatment sequence. See **Error! Reference source not found.**, section A.1.6.3, Table 27 for list of supportive agents, as recorded in BENCHMARK_GROUP.

1.1.6 Data preparation

Data cleaning was carried out before the analyses were conducted to remove patients with missing variables in fields necessary for the analysis. In particular, the following incomplete records were removed:

- Patients with a missing NHS number
- Patients with missing age or sex at MM diagnosis
- Patient with missing vital status information in the CAS database

Data cleaning was performed using R version 4.2.1 by the contracted vendor, IQVIA Ltd.

1.1.6.1 *Masking rules*

To minimise risk of patient re-identification, Health Data Insights (HDI) perform masking such that a level of approximation is applied to all data values in CAS. By avoiding reporting the exact value of small patient numbers, iterative data requests are possible without violating governance standards.

Masking was applied to all study outputs in line with the following rules set out by NHS Digital:

- All small numbers 1-5 are replaced with *.
- Minimum and maximum values are replaced with 5th and 95th percentile values.

1.1.7 Statistical methods

Statistical analyses were performed using R version 4.2.1 by the contracted vendor, IQVIA Ltd.

For patients in the SACT-treated cohort, all recorded SACT treatments were combined into LoTs. Subsequently, regimens were grouped according to the agents that were administered within the first 28 days of the start of the LoT (i.e. those agents that were identified in step A of the LoT algorithm), and this grouping was used for all outputs relating to grouped SACT

regimens. Steroids were not considered when defining the groupings due to the inconsistency with which they were reported in the SACT dataset but would be implicitly captured in the relevant groupings where they were reported.

For each LoT, the five most frequently occurring grouped regimens were subsequently identified among patients who received each LoT; these grouped regimens were used for all outputs stratified by the most commonly occurring SACT regimen groups.

No imputation methods were used to handle missing data; only available data were summarised. No sensitivity analyses were performed.

1.1.8 Bias

The CAS database covers approximately 95% of patients in England who receive systemic cancer treatments. However, due to the exclusion of patients with a record of having received (at any LoT) any treatment which was on the CDF register at the time of analysis, it was expected that the treatment patterns and outcomes observed for study participants would not be wholly representative of those for the more general cohort of SACT-treated patients. While there was no way to minimise the impact of this exclusion, the description of baseline characteristics for the total CDF drugs cohort was included as an exploratory objective to provide some contextualising information (see Section 1.4.1 for further discussion).

For the relevant data presented in this addendum, patients who may have received pomalidomide as a 4th line therapy after progression on a drug in the CDF (at the time of data extraction) at earlier lines may be missing from this dataset and could have contributed useful additional evidence for pomalidomide outcomes in the real world. The impact and direction of any bias due to the masking of CDF treated patients and their outcomes are unquantifiable.

The CAS database does not directly capture LoTs or regimen end dates. To date, there have been no other studies that have sought to derive treatment level, LoT-specific outcomes from SACT in MM. To minimise LoT misclassification, the algorithm was developed iteratively according to treatment guidance with expert clinical input, and data source-specific considerations. Due to the inconsistent recording of steroids and supportive agents in CAS, these were not included as a feature in LoT progression rules. Regimen end dates were calculated based on median cycle duration, which are additionally limited based on available clinical guidelines.

The pre-specified protocol/statistical analysis plan and full final study report are available on request.

1.2 Results

1.2.1 Demographic and clinical characteristics at initiation of 4th line therapy for SACT-treated cohort

Demographic and clinical characteristics at diagnosis for patients in the overall cohort (i.e., all eligible patients with MM who had not received a drug that was on the CDF register at the time of analysis, N=20,240) are provided in **Error! Reference source not found.**.

The SACT-treated cohort was defined such that treatment level outcomes data could be obtained and included patients with MM who received at least one SACT and excluded those who had received (at any LoT) a drug which was not on the CDF list at the time of analysis (N=12,095). Of the SACT-treated cohort available for analysis, 782 patients received 4 or more LoTs; demographic and clinical characteristics at initiation of 4th line for 4th line+ treated patients are provided in Table 6. SACT regimen-specific patient demographic and clinical characteristics were not collected within this study and therefore are not available for patients who received pomalidomide within the 4th LoT. Of the 4th line treated patients in the retrospective study, 182 (23.3%) received pomalidomide, of these outcomes data were available for 175 patients.

In the 4th line+ treated population, the median age at 4th line treatment initiation was 71 years (Q1: 62.00– Q3: 77.00). The is comparable to the median age observed in the CDF cohort of the IsaPd (n=662) and daratumumab (n=2300) SACT cohorts (both 71 years old), whereas the smaller IsaPd SACT EAMS cohort (n=75) had a younger median age (66 years old). Compared with the 4th line SACT treated cohort, the Pd arm reported from the ICARIA-MM trial in the CS, were slightly younger (median: 65.5 years old).

As observed in the other available SACT treatment datasets, ECOG score at 4th line initiation was poorly recorded, with 153 patients (19.6%) having a missing or unknown value for ECOG. Nevertheless, all 606 (77%) patients at 4th line initiation in the retrospective SACT study with non-missing values for ECOG had a score between 0 and 2. (Table 6). This is again comparable with patients reported in the SACT data for IsaPd and daratumumab (range: 72–77%), where data were available. In the ICARIA-MM Pd arm, all patients had an ECOG score between 0 and 2 in line with the trial inclusion criteria.

Table 6: Demographic and clinical characteristics for the retrospective study SACT-treated cohort vs other data source informing the submission

Characteristic	4th line+ SACT-treated cohort	ICARIA-MM 4th line		IsaPd SACT		Dara SACT
		Pd	IsaPd	CDF cohort (IsaPd)	EAMS cohort (IsaPd)	
N	**782**	58	52	662	75	2,301
Age at initiation of 4th line						
N	782	(n=58)	(n=52)	(n=662)	(n=75)	–
Median (Q1 – Q3)	71.00 (62.00–77.00)	65.5	68	71	66	71 (NR)
Percentile 5th – 95th	50.00 – 84.00	–	–	–	–	–
Weight (kg) at initiation of 4th line						
N (%)	752 (96.16)	–	–	–	–	–
Median (Q1 – Q3)	74.45 (64.10–86.00)	–	–	–	–	–
Percentile 5th – 95th	49.00 – 104.22	–	–	–	–	–
ECOG score at initiation of 4th line (N (%))						
0	137 (17.52)	30 (51.7)	21 (40.4)	124 (18.7†)	25 (33.3†)	467 (20)
1	329 (42.07)	23 (39.7)	25 (48.1)	259 (39.1†)	27 (36.0†)	936 (41)
2	140 (17.9)	5 (8.6)	6 (11.5)	92 (13.9†)	6 (8.0†)	341 (15)
3	** (**%)	–	–	5 (0.8†)	0	36 (2)
4	* (*%)	–	–	1 (<0.2†)	0	1 (<1)
Missing/Unknown	153 (19.57)	–	–	181 (27.3†)	17 (22.7†)	520 (23)
Follow-up time from initiation of 4th line (months)						
N	782	–	–	–	–	–
Median (Q1 – Q3)	9.40 (3.12–19.94)	–	–	–	–	–
Percentile 5th – 95th	0.63 – 38.33	–	–	–	–	–

*Number 1–5 are masked, as per CAS reporting rules; **Denotes secondary suppression by HDI; †data taken from SACT report
Abbreviations: CAS, Cancer Analysis System; CDF, Cancer Drugs Fund; Dara, daratumumab; EAMS, early access to medicines scheme; ECOG, Eastern Cooperative Oncology Group; HDI, Health Data Insights; IsaPd, isatuximab plus pomalidomide and dexamethasone LoT, line of therapy; Pd, pomalidomide and dexamethasone; Q, quarter; SACT, Systemic Anti-Cancer Therapy.

1.2.2 Treatment pattern

1.2.2.1 *Distribution of SACT treatments at 4th line*

Of the SACT-treated cohort, 782 patients received 4 or more LoTs. The most common regimen groups received by patients in the SACT-treated cohort at 4th line were daratumumab (N=245, 31.3%), pomalidomide (N=182, 23.3%), and lenalidomide (N=74, 9.5%) (Table 7).

Although 31.3% of the population received daratumumab at 4th line based on this study, these data are not presented due to published data available for the full cohort of patients receiving daratumumab monotherapy at 4th line which have already informed a reimbursement decision and was included in the company submission [ID4067](3).

Therefore, the results presented for outcomes henceforth focuses only on the pomalidomide data at 4th line (N=182), with the number of patients contributing data to each outcome denoted. Results for the other common regimens at 4th line (including daratumumab) are available in **Error! Reference source not found.**.

It is important to contextualise this data given the time period available for study inclusion and available follow-up duration for outcomes. Patients diagnosed between 2014 and 2019 were included, and treatment and survival data were available until May 2021 and Aug 2021, respectively. Furthermore, the data on patients who were receiving a CDF funded therapy at the time of data extraction are masked from any outcomes analysis and hence were excluded from the SACT-treated cohort.

Table 7: Most common regimen groups recorded among patients in the SACT-treated cohort, overall and at 4th line

Regimen group	Total		4th line	
	N	%	N	%
Total number of patients	**19,960**	**100.0**	**782**	**3.9**
Bortezomib + cyclophosphamide†	3,323	16.7	*	*
Lenalidomide†	2,973	14.9	74	9.5
Bortezomib + thalidomide†	2,465	12.4	*	*
Bortezomib†	2,337	11.7	**	**
Cyclophosphamide + thalidomide	1,703	8.5	12	1.5
Trial	1,015	5.1	30	3.8
Bortezomib + melphalan	940	4.7	*	*
Melphalan	826	4.1	12	1.5
Cyclophosphamide	644	3.2	18	2.3
Daratumumab†	606	3.0	245	31.3
Pomalidomide†	473	2.4	182	23.3
Cyclophosphamide + lenalidomide	429	2.2	15	1.9
Melphalan + thalidomide†	368	1.8	*	*
Ixazomib + lenalidomide†	363	1.8	17	2.2
SCT alone	212	1.1	*	*
Bortezomib + panobinostat†	193	1.0	70	9.0
Thalidomide	157	0.8	*	*
Carfilzomib†	120	0.6	*	*
Cisplatin + cyclophosphamide + doxorubicin + etoposide + thalidomide	68	0.34	*	*
Bendamustine + thalidomide	61	0.31	7	0.9

†Denotes regimen of interest; * Values between 1 and 5 have been masked, as per CAS reporting rules;
**Additional values have been masked to prevent back calculation of masked values
Abbreviations: CAS, Cancer Analysis System; SACT, Systemic Anti-Cancer Therapy; SCT, stem cell transplant.

1.2.3 Outcomes

Outcomes data from SACT study are reported below alongside respective data from the IsaPd combined cohort where relevant. Detailed description of the IsaPd SACT data for the combined cohort were discussed in the original company submission [Document B, Section B.2.6.2] and therefore are not discussed in depth within this addendum.

1.2.3.1 *Treatment duration*

Median treatment duration decreased at each LoT and was estimated to be 3.7 months (95% CI: 3.5, 4.3) for patients receiving 4th line treatments.

At 4th line, patients receiving pomalidomide had a median treatment duration of 3.2 months (95% CI: 2.7, 4.1) (Table 8). The data provided for in context for IsaPd are taken directly from the IsaPd SACT report and denotes the combined cohort.

Table 8: Median treatment duration for patients receiving pomalidomide in the SACT-treated cohort at 4th line vs IsaPd SACT Treatment duration

Cohort	Median TD (95% CI)	Number of patients
Pomalidomide SACT	3.2 (2.7, 4.1)	175
IsaPd SACT	8.9 (7.3, 10.8)	736

Abbreviations: CI, confidence interval; IsaPd, isatuximab with pomalidomide and dexamethasone; SACT, Systemic Anti-Cancer Therapy; TD, treatment duration.

Figure 3: Reconstructed SACT Treatment duration – Kaplan-Meier curves by treatment group: IsaPd and Pd

Abbreviations: IsaPd, isatuximab with pomalidomide and dexamethasone; KM, Kaplan-Meier; Pd, pomalidomide plus dexamethasone; SACT, systemic anti-cancer therapy; TTD, time to discontinuation.

1.2.3.2 *Time to next treatment*

Overall, TTNT decreased by an average of 29% at each LoT. Median TTNT was estimated to be 11.2 months (95% CI: 9.9, 13.2) for patients receiving 4th line. Median TTNT was estimated to be 18.8 months (95% CI: 12.9, NA) for patients receiving 4th line pomalidomide in SACT.

TTNT was included initially in the study as one potential estimate for rwPFS, however given that death is not counted as an event variable in this outcome and patients may discontinue treatment for reasons other than progression (e.g., toxicity, patient choice), the estimate of PFS using this outcome was therefore deemed at risk of bias due to left censoring but is nevertheless presented for completeness.

1.2.3.3 *Time to next treatment or death*

For patients receiving treatment with any 4th line therapy, median TTNTD was 5.6 months [95% CI: 4.83, 6.14]. Median TTNTD for patients receiving pomalidomide at 4th line was 4.70 [95% CI: 3.9, 5.98]. Equivalent data for this endpoint was not available from the IsaPd SACT data.

Table 9: Median TTNTD for patients receiving pomalidomide in the SACT-treated cohort at 4th line

Cohort	Median TTNTD, months (95% CI)	Number of patients
Pomalidomide SACT	4.70 (3.91, 5.98)	175

Abbreviations: CI, confidence interval; IsaPd, isatuximab with pomalidomide and dexamethasone; SACT, Systemic Anti-Cancer Therapy; TTNTD, time to next treatment or death.

1.2.3.4 *Overall survival*

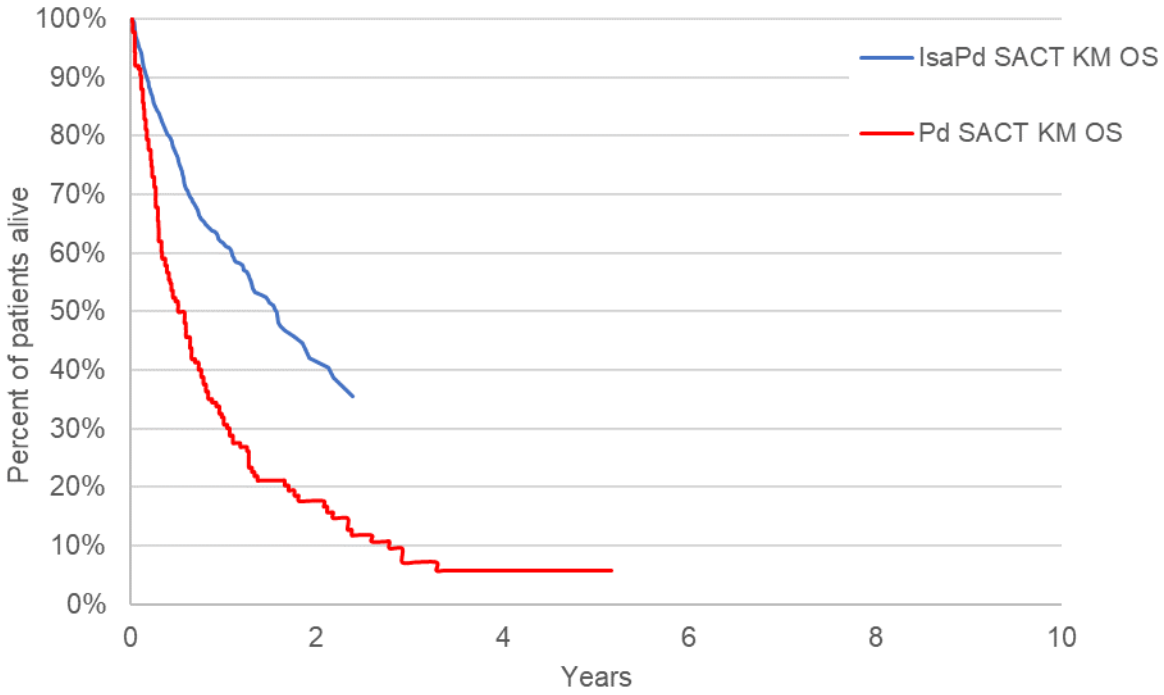
For patients receiving 4th line treatment with any therapy, median OS was 11.5 months (95% CI: 9.8, 13.4). In patients receiving pomalidomide, median OS was 6.3 months (95% CI: 4.6, 7.8).

Table 10: Median Overall survival for patients receiving pomalidomide in the SACT-treated cohort at 4th line vs IsaPd SACT OS

Cohort	Median OS, months (95% CI)	Number of patients
Pomalidomide SACT	6.3 (4.6, 7.8)	175
IsaPd SACT	18.8 (15.7, 22.9)	736

Abbreviations: 4th line, 4th line; CI, confidence interval; IsaPd, isatuximab with pomalidomide and dexamethasone; OS, overall survival; SACT, Systemic Anti-Cancer Therapy.

Figure 4: Reconstructed SACT Overall survival - Kaplan-Meier curves by treatment group: IsaPd and Pd



Abbreviations: IsaPd, isatuximab with pomalidomide and dexamethasone; KM, Kaplan-Meier; OS, overall survival; Pd, pomalidomide plus dexamethasone; SACT, systemic anti-cancer therapy.

1.3 RWE Data Suitability Assessment Tool (DataSAT)

The full RWE Data Suitability Assessment Tool (DataSAT) assessment is provided in **Error! Reference source not found.**.

1.4 Interpretation and relevance of the additional clinical effectiveness evidence

In this retrospective study using NCRAS, the duration of treatment and clinical survival outcomes for patients with MM decreased with each subsequent LoT received, which is aligned to the current understanding of the disease and outcomes for MM patients. Data from the SACT database, reflecting the real-world complexity of MM treatment in England, included 782 patients in the 4th line cohort with a median age of 71 at 4th line treatment initiation, and majority (77%) of patients had generally good ECOG functional status (score between 0 and 2), where data were documented.

Real world OS and PFS estimates for Pd from two older UK studies identified in the targeted literature review (TLR [**Error! Reference source not found.**]) was 10.9 months for OS in patients at 4th line (vs 6.3 months presented here) (4, 5), and median PFS (proxied here by median TTNTD: 4.7 months) estimates after three prior lines of 3.4 months in clinical practice (4). These differences in outcomes compared to other published sources may be influenced by their study design, small sample sizes patient characteristics or the differences in available subsequent therapies at the time of the study.

1.4.1 Strengths and limitations

SACT data provide RWE on prescribed therapy outcomes. While IsaPd data was available from the CDF, Pd data from SACT was lacking. This analysis used RWE from England for both Pd and IsaPd from the SACT database, providing pertinent evidence from the same source (NCRAS-SACT) and reflecting clinical practice. Although the comparison may seem naïve, rwPFS from SACT (median PFS: 4.70 months (95% CI: 3.91, 5.98)) is consistent with PFS from the Pd randomised control trial (RCT) MM-003 (median PFS: 4·0 months (95% CI: 3·6, 4·7)) but highlights the discrepancy in rwOS. Median rwOS: 6.3 months (95%CI: 4.6, 7.8)) influenced by subsequent therapies in clinical practice, understandably shows less favourable outcomes compared to the trial data for the Pd arm from both MM-003 and ICARIA-MM trials (median OS: 12·7 months in the ITT population (95% CI 10.4–15.5) and 17.71 months (95% CI: 11.57, 27.53) in the 4th line subgroup, respectively).

It is important to note that study results are descriptive, and differences in outcomes associated with treatment regimens could be due to patient characteristics rather than the treatments themselves. This has been discussed as a limitation previously regarding the use of SACT data. However, it is reassuring that the patient characteristics observed across the SACT datasets (4th LoT SACT [Pom], IsaPd SACT and daratumumab monotherapy SACT) are broadly comparable, where data is available. Furthermore, the results from this study for daratumumab are also reassuringly consistent with the data reported in the DARA SACT report (6), although the latter more complete data were used in the exploratory analyses presented in the company submission. This is not unexpected given that these data were derived from the same underlying source and all treatments are available at 4th line in clinical practice and provides confidence in the observed Pd data from this retrospective study.

The grouping of regimens based on drugs administered in the first 28 days of treatment results in heterogeneous regimen groups, making it challenging to compare them with other studies and treatment guidelines. In addition, the recorded treatments in the SACT database were combined into LoT using an algorithm that was developed with input from national and international treatment guidance and clinical expertise. However, some misclassification of LoTs is expected due to deviations from recommended treatments, unexpected delays, or inaccuracies in recording, as perhaps expected in routine clinical practice.

Corticosteroid therapies are not systematically recorded in the database and were excluded from treatment grouping rules to maintain consistency across LoT regimens. Clinical expert input during study development confirmed that it is highly likely that most regimens included corticosteroids and their omission should not be interpreted as a lack of their use. This omission is especially challenging for chemotherapy agents that can be delivered with or without steroids, as the data does not distinguish between these regimens.

The exclusion of 4,089 patients who received drugs through the CDF may have altered the composition of the study population and is an ongoing limitation of any real-world study conducted using the NCRAS data. CDF treated patients were generally younger, diagnosed more recently, had lower comorbidity scores, and better functional status. Consequently, the remaining population may be skewed toward individuals with poorer performance status (although the 4th LoT characteristics from SACT suggested that majority of patients for whom data were recorded had ECOG <2), who typically face worse outcomes and are less likely to

reach the 4th line. Yet, the impact of excluding CDF-treated patients on the identification of individuals receiving pomalidomide at the 4th line, the potential differences in outcomes compared to those included in the evidence, and the overall direction of any effects remain unclear.

1.5 Conclusions

In summary, the analysis leverages robust data but acknowledges limitations related to the descriptive nature of results, challenges in regimen grouping, and potential impact of excluding CDF-treated patients. Despite these limitations, the strengths of the analysis lie in its alignment with UK real-world practices and the consistent use of a comprehensive database. Therefore, these Pd SACT data can facilitate an informative comparative analysis to be presented using SACT data for both IsaPd and Pd, which is more reflective of real-world outcomes for patients receiving IsaPd or Pd treatment at 4th line in England.

2 Use in the economic model

As noted by the EAG in its report, the use of subsequent daratumumab in the ICARIA-MM trial (which is not consistent with the UK pathway) introduces uncertainty in the measurement of OS, the relative treatment effect observed in the ICARIA-MM trial and could impact the generalisability of the trial results to the UK context.

This addendum uses treatment duration and overall survival endpoints from the 4th line pomalidomide SACT data, outcomes most consistent with existing SACT analyses provided by NHS Digital, to assess the cost effectiveness of IsaPd vs Pd.

Despite unavailability of individual patient level data and limited reported baseline characteristics for adjustment, this data enables the use of outcomes observed in the real world for both therapies and improves the generalisability of the overall evidence to UK practice.

2.1 Model amends to accommodate Pd SACT data and comparison vs IsaPd SACT

Of the available time to event outcomes from Pd SACT, treatment duration and OS are used within the economic model to enable a comparison of IsaPd SACT vs Pd SACT. Treatment duration is assumed to be equivalent to time to treatment discontinuation (TTD) and PFS (PFS-on treatment curve is equal to the TTD curve), aligning to the assumption used for IsaPd SACT and accepted by the EAG.

During the process of incorporating the Pd SACT data, the model start age for this comparison has been updated to better reflect the population from which the real-world treatment effectiveness estimate is obtained and subsequently informing the model. The updated model start age used in the comparison of IsaPd SACT vs Pd SACT is therefore 71.0 years aligned to the median age in the 4th line population from the NCRAS data and the CDF cohort (largest cohort) of IsaPd SACT.

To alleviate previous EAG concerns on the lack of alignment between the interventions generating survival and the cost of interventions, the model uses the subsequent therapy

data from IsaPd SACT for both treatment arms. The treatment options at 5th line have remained relatively unchanged and since IsaPd contains the Pd component, it is reasonable to assume that the subsequent therapies available to Pd patients would not be dissimilar to those that are received after IsaPd in SACT.

No other changes have been made to the base case model inputs in incorporating the Pd SACT data. A revised model with the Pd SACT analysis incorporated has been provided to accompany this addendum.

2.2 Survival extrapolations

The KM curves for treatment duration (TTD) and OS for Pd SACT were digitised. For both OS and TTD, all standard parametric models (exponential, Weibull, Gompertz, log-logistic, lognormal, gamma, generalised gamma, and generalised F distributions) and three spline models with one knot (RCS lognormal, RCS Weibull and RCS log-logistic) were fitted independently to Pd SACT data. As per response to clarification question B13, and aligned to those considered for IsaPd, extrapolations using spline models with two and three knots were additionally considered for Pd SACT. Curve selection for Pd SACT followed the same process outlined in the CS Section B.3.3.2.1 and sought clinical opinion for OS where there is greater uncertainty (discussed below in Section 2.2.3).

The fits considered for IsaPd SACT were those presented in the company submission and those additionally provided in response to EAG clarification questions.

2.2.1 Pd SACT – Treatment duration/TTD

The TTD KM and hazard rate for the Pd SACT population are reported in Figure 5 and fit statistics are reported in Table 11.

Figure 5. TTD – Pd SACT population

A. Kaplan-Meier Survival Distribution	B. Hazard Rates
[redacted]	

Abbreviations: Pd, pomalidomide + dexamethasone; SACT, systemic anti-cancer therapy; TTD, time to treatment discontinuation.

Table 11. Fit Statistics, TTD, Pd SACT population

Distribution	DF	-2LL	AIC	AICc	BIC
Gompertz	2	795.1	799.1	799.2	805.5
Log-Logistic	2	795.3	799.3	799.4	805.7
Lognormal	2	799.5	803.5	803.6	809.8

Distribution	DF	-2LL	AIC	AICc	BIC
RCS Log-Logistic	3	794.5	800.5	800.6	810.0
RCS Weibull	3	796.3	802.3	802.4	811.7
Gen. Gamma	3	799.3	805.3	805.4	814.8
RCS Lognormal	3	799.4	805.4	805.5	814.9
Gen. F	4	794.3	802.3	802.5	815.0
RCS Log-Logistic 2k	4	794.4	802.4	802.7	815.1
RCS Weibull 2k	4	794.9	802.9	803.1	815.6
RCS Lognormal 2k	4	796.2	804.2	804.4	816.8
RCS Weibull 3k	5	792.6	802.6	803.0	818.4
RCS Log-Logistic 3k	5	793.8	803.8	804.2	819.7
RCS Lognormal 3k	5	794.8	804.8	805.2	820.7
Weibull	2	829.1	833.1	833.2	839.5
Gamma	2	841.8	845.8	845.9	852.2
Exponential	1	855.7	857.7	857.7	860.9

Abbreviations: -2LL, -2 log-likelihood; AIC, Akaike Information Criterion; AICc, corrected Akaike Information Criterion; BIC, Bayesian Information Criterion; DF, degrees of freedom; Gen, generalise; k, knot; RCS, restricted cube spline; TTD, time to treatment discontinuation.

Parametric survival distributions for TTD out to 20 years for all fitted distributions are shown in Figure 6. These curves do not consider general population mortality or constraint to avoid PFS/TTD from exceeding OS at any given time point, these constrains are applied within the model for all distributions.

Figure 6. Parametric survival distributions fit to TTD to 20 years –Pd SACT population

Abbreviations Gen. generalised; Pd, pomalidomide + dexamethasone; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy; TTD, time to treatment discontinuation.

Hazard rates during follow-up for the top six best fitting parametric survival distributions based on BIC for TTD are compared with non-parametric hazards in Figure 7. Long-term projections of TTD hazard rates (to 20 years) for these six distributions are shown in Figure 8.

Figure 7. Hazard rates for parametric survival distributions fit to TTD in the time period of data availability – Pd SACT population

Abbreviations: Gen. generalised; Pd, pomalidomide + dexamethasone; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy; TTD, time to treatment discontinuation.

Figure 8. Hazard rates for parametric survival distributions fit to TTD over 20 years– Pd SACT population

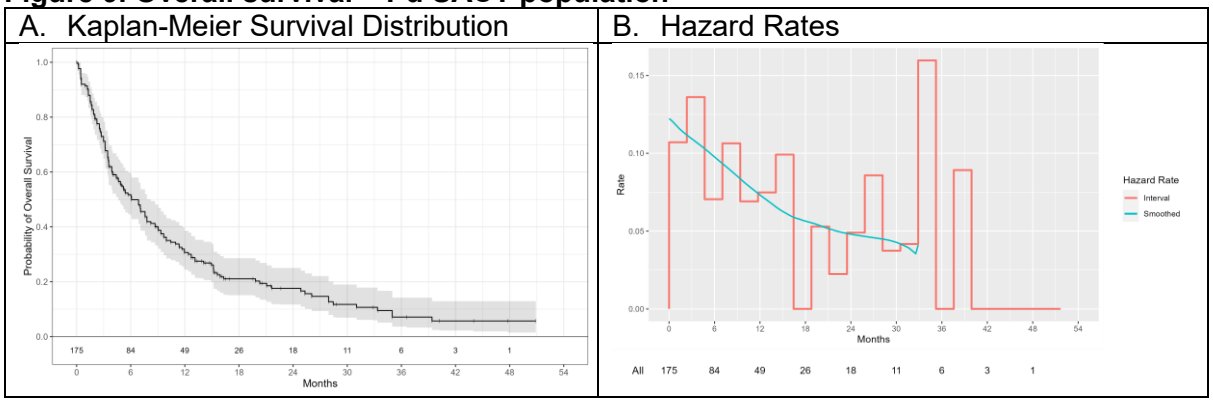
Abbreviations: Gen, generalised; Pd, pomalidomide + dexamethasone; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy; TTD, time to treatment discontinuation, overall survival.

The statistically best fitting Gompertz curve implied that patients would remain on treatment for a significant timeframe although the median TTD was <4 months. Therefore, the Log-Logistic curve was chosen as the base case TTD curve for Pd SACT since it provided a more plausible long-term time on treatment assumption whilst retaining reasonably good fit to the observed data. Alternative curve choices of Lognormal or RCS Log-Logistic which also had reasonably good statistical and visual fit to the data are tested in scenario analyses.

2.2.2 Pd SACT – Overall survival

The OS KM and hazard rate for the Pd SACT population are reported in Figure 9 and fit statistics are reported in Table 12.

Figure 9. Overall survival – Pd SACT population



Abbreviations: Pd, pomalidomide + dexamethasone; SACT, systemic anti-cancer therapy.

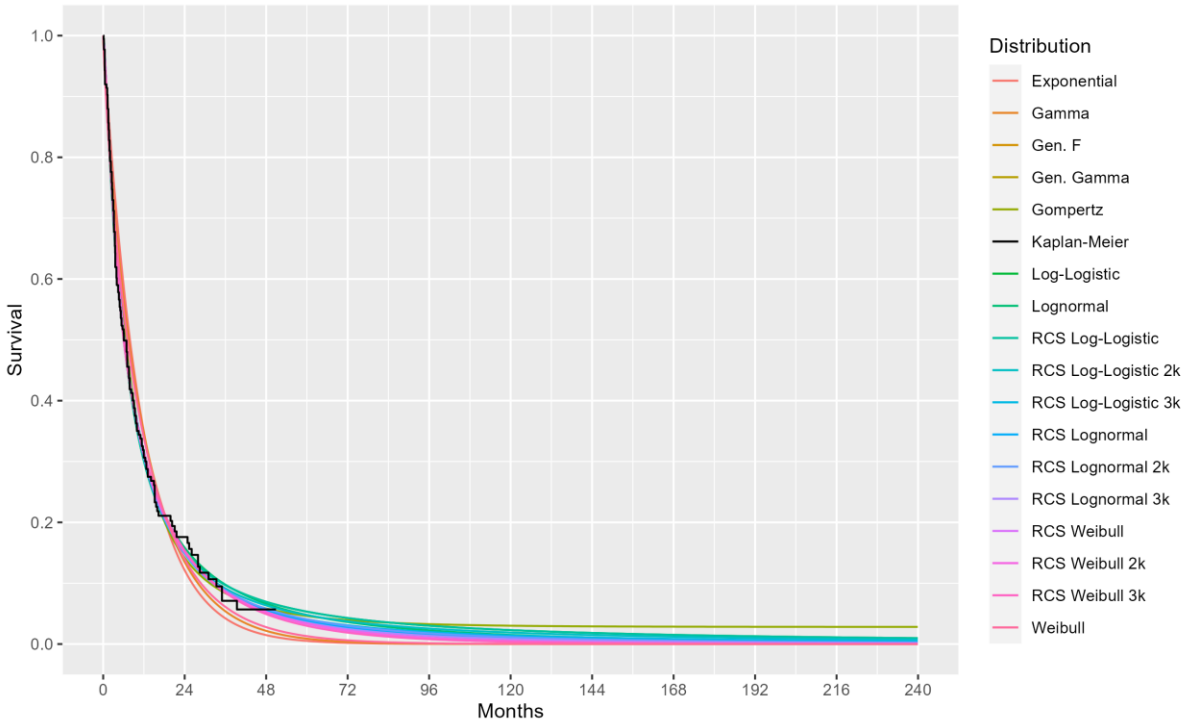
Table 12. Fit Statistics, OS, Pd SACT population

Distribution	DF	-2LL	AIC	AICc	BIC
Lognormal	2	988.1	992.1	992.1	998.4
Log-Logistic	2	988.2	992.2	992.2	998.5
Gompertz	2	990.5	994.5	994.6	1,000.9
RCS Lognormal	3	987.0	993.0	993.2	1,002.5
RCS Weibull	3	987.0	993.0	993.1	1,002.5
Gen. Gamma	3	987.1	993.1	993.2	1,002.6
RCS Log-Logistic	3	988.2	994.2	994.3	1,003.7
Weibull	2	996.5	1,000.5	1,000.5	1,006.8
Exponential	1	1,002.0	1,004.0	1,004.0	1,007.1
RCS Lognormal 2k	4	986.9	994.9	995.1	1,007.5
Gen. F	4	987.1	995.1	995.3	1,007.7
RCS Weibull 2k	4	987.1	995.1	995.3	1,007.7
RCS Log-Logistic 2k	4	987.8	995.8	996.1	1,008.5
Gamma	2	999.0	1,003.0	1,003.0	1,009.3
RCS Lognormal 3k	5	985.9	995.9	996.2	1,011.7
RCS Weibull 3k	5	986.3	996.3	996.7	1,012.1
RCS Log-Logistic 3k	5	986.5	996.5	996.9	1,012.4

Abbreviations: -2LL, -2 log-likelihood; AIC, Akaike Information Criterion; AICc, corrected Akaike Information Criterion; BIC, Bayesian Information Criterion; DF, degrees of freedom; Gen, generalise; k, knot; OS, overall survival; Pd, pomalidomide + dexamethasone; RCS, restricted cube spline.

Parametric survival distributions for OS extrapolated to 20 years for all fitted distributions are shown in Figure 10

Figure 10. Pd SACT- Parametric survival distributions for OS fit to 20 years

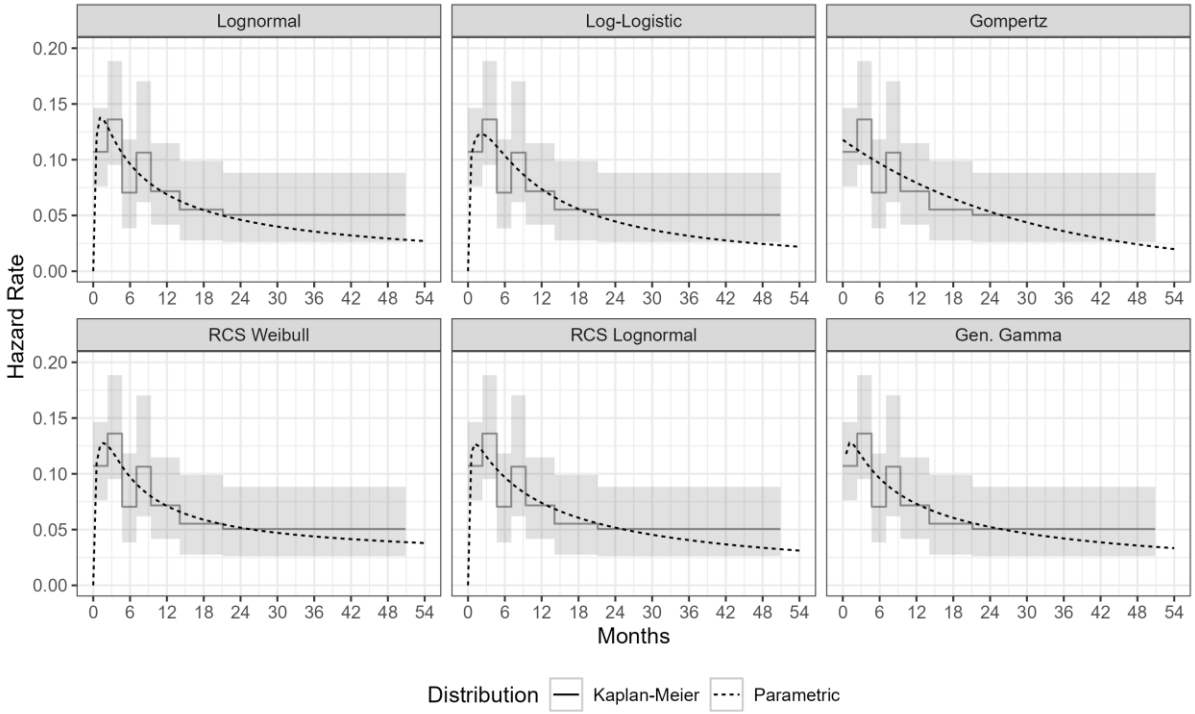


Abbreviations: Gen. generalised; Pd, pomalidomide + dexamethasone; OS, overall survival; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy.

Hazard rates during follow-up for the top six best fitting parametric survival distributions based on BIC for OS are compared with non-parametric hazards in Figure 11. Long-term projections of hazard rate for OS (to 20 years) for these six distributions are shown in Figure 12. The full set of distributions considered for Pd SACT OS are provided in Pd SACT OS-Statistical fits and additional distribution.

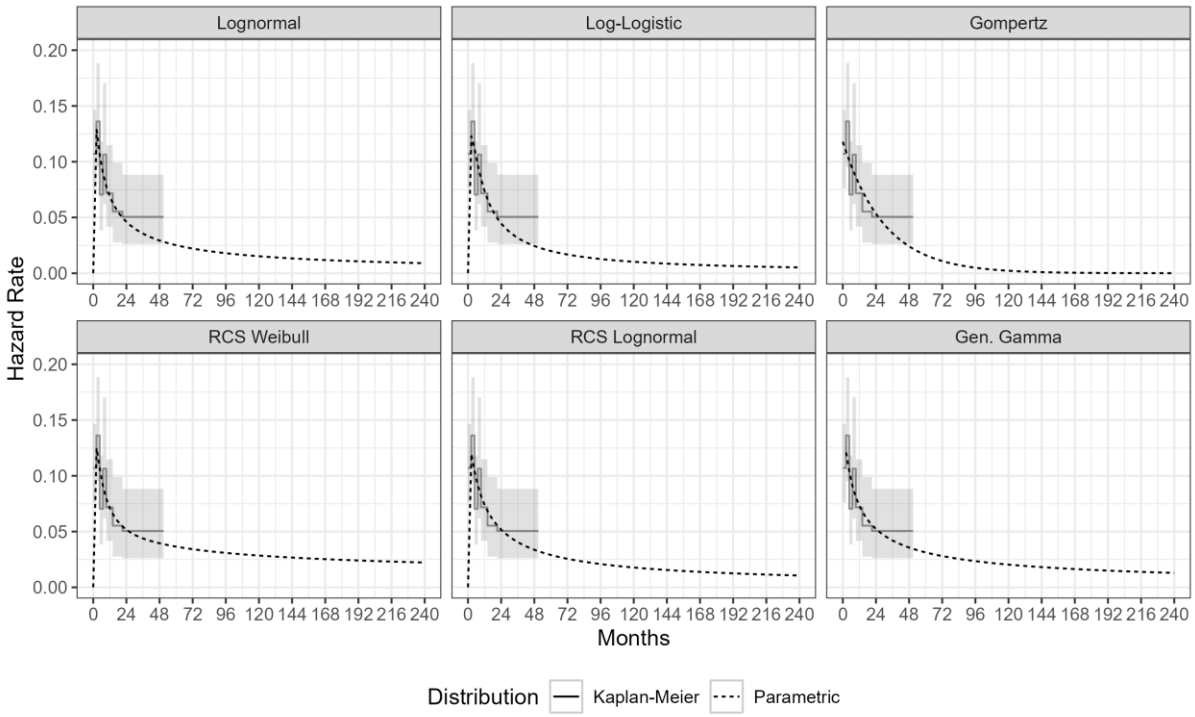
The review of fit statistics suggests that the independently fitted Lognormal would be a good fit with the lowest AIC and BIC scores and a clinically reasonable tail survival. Other distributions with reasonable statistical and visual fits included the RCS Weibull, RCS Lognormal and Generalised Gamma distributions.

Figure 11. Hazard rates for parametric survival distributions fit to OS in the time period of data availability – Pd SACT population



Abbreviations: Gen. generalised; IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy.

Figure 12. Hazard rates for parametric survival distributions fit to OS over 20 years– Pd SACT population



Abbreviations: Gen, generalised; Pd, pomalidomide + dexamethasone; OS, overall survival; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy.

2.2.3 Clinical validation of OS expected for IsaPd and Pd using available SACT data

The use of SACT data from the real-world study for the comparison of IsaPd vs Pd and the expected overall survival were validated in individual consultations with three myeloma clinical experts in November 2023. These experts were independently asked to provide a range of plausible proportion of patients that are likely to be alive (or distributions that fit the plausible ranges) at various timepoints post 4th line treatment with either IsaPd or Pd. The proportion of patients alive at different timepoints based on the individual parametric survivals were shown to the clinical experts alongside the available KM data (Table 13 and Table 14). The distributions used in the validation had general population mortality applied so that survival could never exceed that observed in the general population at any given timepoint.

2.2.3.1 *IsaPd SACT OS*

A range of plausible survival times were discussed for IsaPd, with clinicians providing a wide range and advising up to 25% of patients being alive at 5 years. By 10 years, clinicians estimated that fewer than 10% of patients may remain alive but discussed that this depends on the more novel therapies that patients receiving IsaPd can bridge onto at 5th line+ (such as CAR-T therapy/Belantamab mafodotin) which could improve survival overall. They also re-iterated that most of the treatment with IsaPd in CDF had occurred during COVID-19 period which may have negatively impacted the overall outcomes currently observed for IsaPd in SACT.

The feedback from clinicians for IsaPd were wide-ranging and inconsistent, reflecting the challenge of predicting long term benefit of a treatment for which they have limited experience and where the sequencing options for treatment at 5th line are evolving. However, based on the discussions and after visually assessing distributions, the upper range estimate preferred by clinicians for IsaPd survival aligned most closely with the Log-Logistic curve (2nd best fit), however this range could also support the lognormal curve (5 year survival: ~25%) which also has the best statistical fit (Figure 13). Whilst RCS Lognormal 2k represented a mid-range extrapolation and RCS Weibull 2k or Weibull represented worst-case survival, these curves do not align as closely to the KM data (Table 13). Therefore, the base case curve chosen to model survival for IsaPd is the best statistically fitting independent Lognormal distribution, which remains within the clinically plausible range based on clinical feedback to the company.

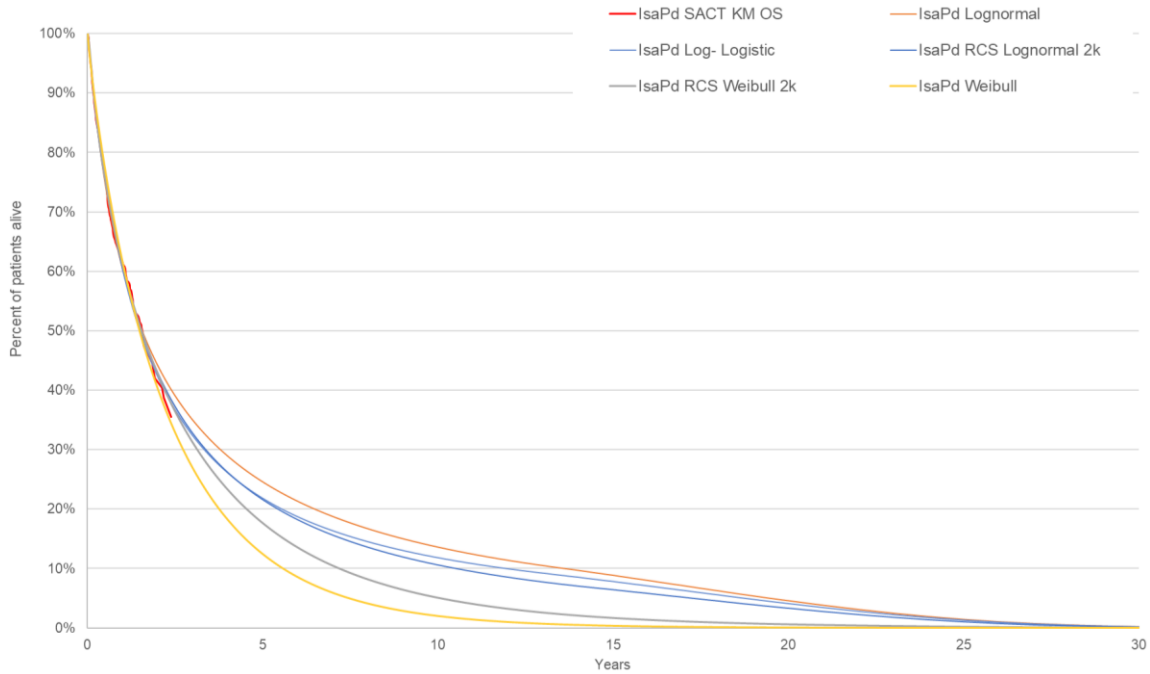
Table 13. IsaPd SACT- Proportion of patients alive by time

	Proportion of patients alive by time (Years)						
Distribution	**1**	**2**	**3**	**5**	**10**	**15**	**30**
KM survival	*62%*	*42%*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*
Lognormal OS	60.59%	44.35%	35.11%	24.59%	13.61%	9.04%	1.31%
Log-Logistic	60.61%	42.50%	32.49%	21.83%	11.83%	8.04%	1.19%
Gen. Gamma	60.61%	44.16%	34.78%	24.10%	13.03%	8.49%	1.22%
RCS Lognormal	60.60%	44.13%	34.76%	24.15%	13.16%	8.65%	1.25%

	Proportion of patients alive by time (Years)						
Distribution	**1**	**2**	**3**	**5**	**10**	**15**	**30**
Gompertz	60.75%	43.29%	34.38%	26.38%	21.56%	18.12%	2.73%
RCS Weibull	60.73%	43.70%	33.18%	20.43%	7.47%	3.15%	0.25%
RCS Log-Logistic	60.54%	44.48%	35.53%	25.52%	15.31%	11.06%	1.66%
Exponential	61.87%	38.27%	23.68%	8.98%	0.81%	0.07%	0.00%
RCS Lognormal 2k	61.03%	43.16%	32.91%	21.62%	10.62%	6.46%	0.89%
RCS Weibull 2k	61.20%	42.89%	31.29%	17.61%	5.06%	1.67%	0.08%
RCS Log-Logistic 2k	61.07%	43.14%	33.01%	22.16%	11.98%	8.12%	1.20%
Gen. F	60.60%	44.16%	34.77%	24.10%	13.04%	8.50%	1.22%
Weibull	61.66%	40.40%	27.01%	12.41%	2.00%	0.35%	0.00%
Gamma	61.81%	39.86%	25.96%	11.07%	1.38%	0.17%	0.00%
RCS Weibull 3k	60.63%	43.57%	33.35%	20.93%	8.06%	3.59%	0.32%
RCS Log-Logistic 3k	60.53%	43.89%	34.80%	24.73%	14.60%	10.44%	1.56%
RCS Lognormal 3k	60.54%	43.84%	34.53%	24.00%	13.10%	8.62%	1.24%

Abbreviations: Gen, generalised; k, knot; N/A, not available; Pd, pomalidomide + dexamethasone; OS, overall survival; RCS, restricted cubic spline; SACT, systemic anti-cancer therapy.

Figure 13. Potential range of OS with IsaPd SACT



Abbreviations: Gen, generalised; IsaPd, isatuximab + pomalidomide + dexamethasone; k, knot; KM, Kaplan-Meier; OS, overall survival; RCS, restricted cubic spline; SACT, systemic anti-cancer therapy.

2.2.3.2 *Pd SACT OS*

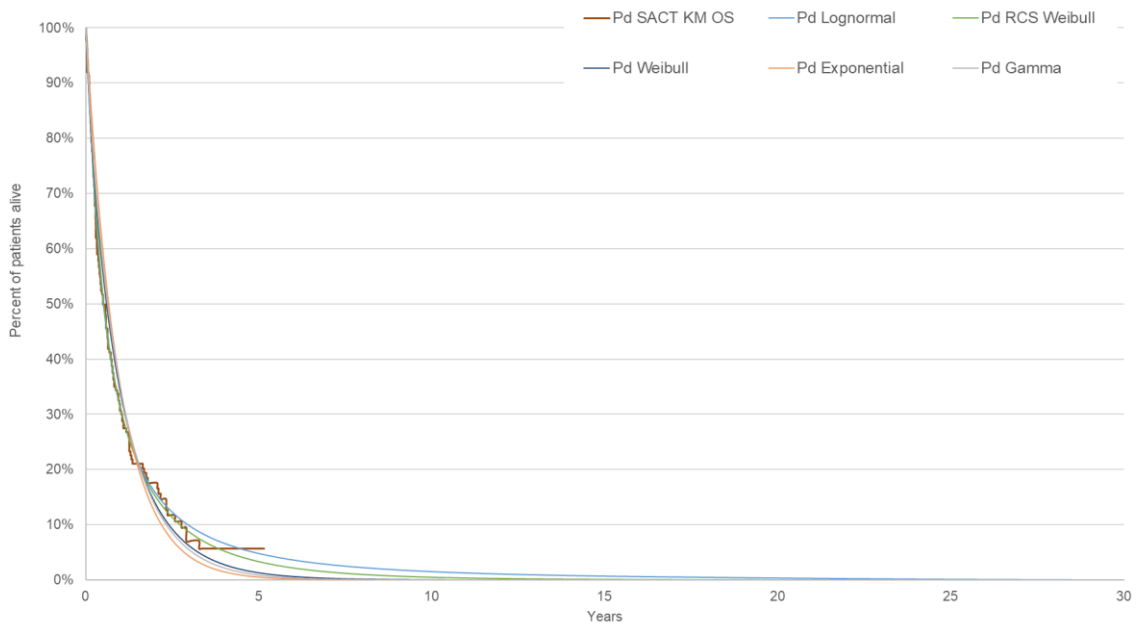
Following a similar discussion for Pd SACT overall survival, all three clinical experts expected 0-5% patients to be alive after 5 years post 4th line Pd treatment (Table 14). This was despite considering current treatment practice or availability of improved treatment options at 5th line in future. The clinicians preferred distributions such as RCS Weibull for an upper range and Gamma, Weibull or Exponential distributions as their mid-lower range extrapolations for Pd OS (Figure 14). There was generally more consistency in their estimation for Pd survival, presumably reflecting their significant experience using this regimen and the relatively complete data available from Pd SACT. With over three years of KM data available from Pd SACT, the survival extrapolation preferred by the clinicians and that most closely aligns with the available data is the RCS Weibull, however given that the lognormal had the best fit to the KM data, we have chosen this distribution in the base case for Pd as a conservative assumption. A selection of distributions preferred by clinicians for Pd have been tested in scenario analyses to assess the impact of assuming poorer outcomes for Pd on the cost-effectiveness.

Table 14. Pd SACT OS- Proportion of patients alive by time

Distribution	1	2	3	5	10	15	30
KM survival	31%	18%	7%	n/a	n/a	n/a	n/a
Lognormal	31.00%	15.90%	9.81%	4.79%	1.51%	0.69%	0.15%
Log-Logistic	30.14%	15.23%	9.72%	5.32%	2.29%	1.38%	0.58%
Gompertz	31.21%	14.24%	8.39%	4.61%	3.01%	2.84%	2.82%
RCS Lognormal	31.14%	14.94%	8.64%	3.80%	0.99%	0.40%	0.07%
RCS Weibull	31.17%	15.25%	8.65%	3.31%	0.49%	0.10%	0.00%
Gen. Gamma	31.28%	15.02%	8.58%	3.59%	0.81%	0.28%	0.03%
RCS Log-Logistic	30.14%	15.24%	9.73%	5.33%	2.29%	1.39%	0.58%
Weibull	33.96%	14.02%	6.16%	1.30%	0.04%	0.00%	0.00%
Exponential	34.95%	12.21%	4.27%	0.51%	0.00%	0.00%	0.00%
RCS Lognormal 2k	30.75%	15.01%	8.89%	4.07%	1.14%	0.48%	0.09%
Gen. F	31.26%	15.02%	8.59%	3.61%	0.82%	0.29%	0.03%
RCS Weibull 2k	31.08%	15.22%	8.68%	3.36%	0.51%	0.11%	0.00%
RCS Log-Logistic 2k	30.70%	14.95%	9.17%	4.75%	1.89%	1.09%	0.43%
Gamma	34.73%	13.58%	5.43%	0.88%	0.01%	0.00%	0.00%
RCS Lognormal 3k	31.71%	15.19%	8.52%	3.52%	0.82%	0.30%	0.04%
RCS Weibull 3k	31.58%	15.45%	8.48%	2.99%	0.35%	0.06%	0.00%
RCS Log-Logistic 3k	31.77%	14.95%	8.61%	4.05%	1.41%	0.76%	0.26%

Abbreviations: Gen, generalised; k, knot; Pd, pomalidomide + dexamethasone; OS, overall survival; RCS, restricted cubic spline; SACT, systemic anti-cancer therapy.

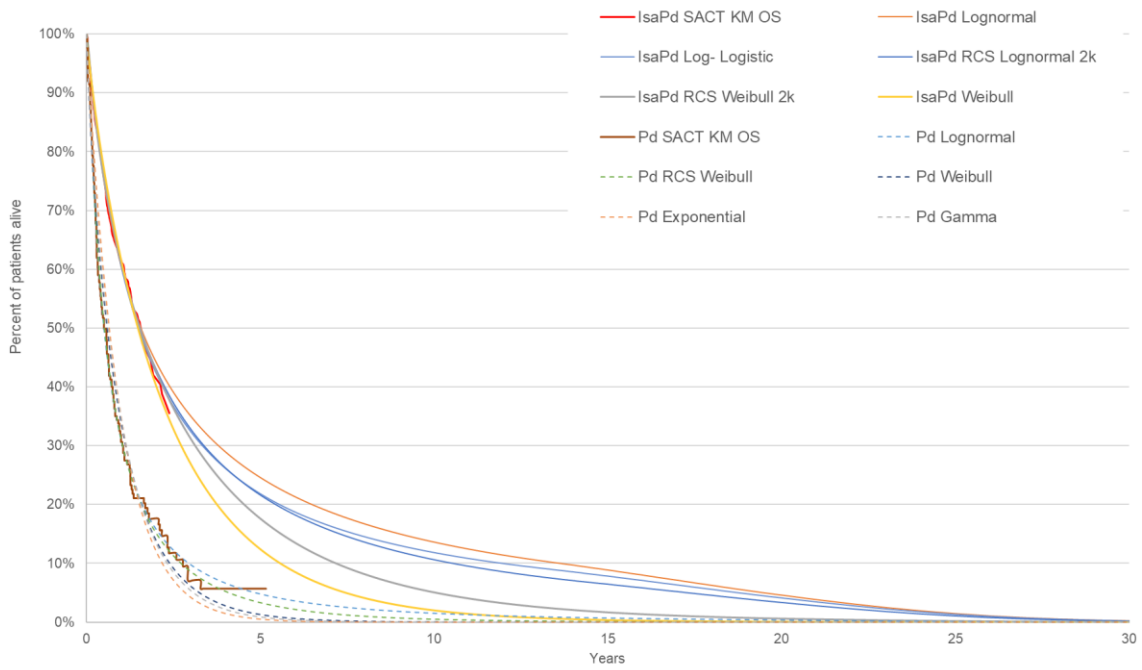
Figure 14. Potential range of OS with Pd SACT



Abbreviations: Gen, generalised; k, knot; KM, Kaplan-Meier; OS, overall survival; Pd, pomalidomide + dexamethasone; RCS, restricted cubic spline; SACT, systemic anti-cancer therapy.

Combined graph demonstrating the possible range for OS across the best fitting and clinician choice curves for IsaPd and Pd SACTs have been presented in Figure 15.

Figure 15. Potential range for OS with IsaPd and Pd SACT- Combined



Abbreviations: Gen, generalised; IsaPd, isatuximab + Pd; k, knot; KM, Kaplan-Meier; OS, overall survival; Pd, pomalidomide + dexamethasone; RCS, restricted cubic spline; SACT, systemic anti-cancer therapy.

In the absence of long-term data for IsaPd, limited clinical experience and implicit assumption that longer PFS should result in longer OS if subsequent therapy choices are similar, the best fitting curve (lognormal) for IsaPd is used. Pd curve used in the company base case can be considered a conservative option since the clinical experts provided generally more pessimistic distributions but aligns with the EAGs preference to use the best fitting distribution for the standard of care therapy.

2.3 Updated base-case ICER vs Pd (SACT vs SACT naïve comparison) (deterministic)

Updated company base-case results for the naïve comparison of IsaPd SACT vs Pd SACT considering a [redacted] PAS for isatuximab only are presented (Table 15). Discounts for other relevant therapies including comparators and subsequent treatments have not been accounted for in the results presented below (unless otherwise stated) and do not reflect the true cost-effectiveness of IsaPd vs Pd. As in the original company submission, additional non-reference case analyses are presented. the backbone cost of Pd in the IsaPd arm in the period in which patients are receiving Pd in both arms (

Table 16) and assuming a [redacted] to the list price of pomalidomide to estimate the cost-effectiveness of IsaPd when a generic version of pomalidomide may be available (Table 17). ICERs using estimated confidential discounts for other therapies and [redacted] for the base case and non-reference case analyses can be found in **Error! Reference source not found.**, Table 38 to Table 40.

The base case deterministic analysis derives an incremental cost of [redacted] for an incremental QALY benefit of [redacted] for IsaPd vs Pd. The total QALYs estimated for Pd is notably worse compared to that generated from the ICARIA-MM trial data reflecting the poorer outcomes observed in the SACT for Pd.

Table 15. Base-case results (deterministic) vs Pd SACT

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	124,744

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; Pd, pomalidomide + dexamethasone; PAS, patient access scheme; QALY, quality-adjusted life year

Table 16. Base case results vs Pd SACT – pomalidomide and dexamethasone backbone cost removed

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	70,291

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; Pd, pomalidomide + dexamethasone; QALYs, quality-adjusted life years.

Table 17. Base case results vs Pd SACT – generic pomalidomide available†

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	53,378

†Discount of [redacted] of pomalidomide assumed
Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; Pd, pomalidomide + dexamethasone; QALYs, quality-adjusted life years.

2.4 Exploring uncertainty

2.4.1 Updated base-case ICER vs Pd (SACT vs SACT naïve comparison) (probabilistic)

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA) in which all parameters are assigned distributions and varied jointly. 1,000 Monte Carlo simulations were recorded, after which the ICER remains stable. Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution and results were plotted on a cost-effectiveness plane.

Results for PSA of IsaPd vs Pd are presented in Table 18. The average incremental costs over the simulated results were [redacted] and the average incremental QALYs were [redacted], resulting in a probabilistic ICER of £125,932, when considering a PAS discount for isatuximab only.

Table 18. Base-case results (probabilistic) vs Pd SACT

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	125,932

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; Pd, pomalidomide + dexamethasone; PAS, patient access scheme; QALY, quality-adjusted life year

The scatter plot of simulations on the cost-effectiveness plane for IsaPd SACT vs Pd SACT is presented in Figure 16. PSA results for the non-reference case analyses, removing the backbone cost of pomalidomide and dexamethasone, and adjusting for the availability of generic pomalidomide are presented in **Error! Reference source not found.**.

Figure 16. Scatter plot of simulations on cost-effectiveness plane - IsaPd SACT vs Pd SACT

2.4.2 Deterministic sensitivity analysis

The results of deterministic sensitivity analysis vs Pd are presented in Figure 17. Parameters were varied by 95% confidence intervals where available, or +/- 25% of the mean value. As the two parameters with the greatest impact on results is the pomalidomide medication costs in IsaPd and Pd, alternative analysis considering patent expiry for pomalidomide were presented in Section 2.3.

Figure 17. Deterministic sensitivity analysis - IsaPd SACT vs Pd SACT

2.4.3 Scenario analysis

2.4.3.1 *Deterministic scenario analysis*

Deterministic scenario analyses were performed to explore the impact of varying key structural assumptions on results. A summary of presented scenario analyses and results are provided in Table 19. The results consider the applicability of the PAS for isatuximab only, all other therapies are considered at list price. Results including estimated confidential comparator discounts and [redacted] are provided in **Error! Reference source not found.**, Table 44.

The scenario with the largest impact on the ICER (+£13,000/QALY) is that where a mid-range survival distribution for IsaPd SACT OS (RCS log-normal 2k) and an optimistic assumption on survival for Pd SACT OS (RCS Weibull) based on clinical validation are used. The largest positive impact scenario is one where no medication wastage is assumed.

Table 19. Scenario analysis (Deterministic): IsaPd SACT vs Pd SACT

Scenario name	Description	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Base case	-	[redacted]	[redacted]	124,744
No medication wastage	Weight- and BSA-based drug vials can be shared between patients	[redacted]	[redacted]	99,076
Other costs from DARA NICE submission	**On-Therapy Progression-Free Resource use** Physician visit: 23% Complete blood count test: 21% Biochemistry: 19% **Off-Therapy Progression-Free Resource Use** Physician visit: 8% Complete blood count test: 21% Biochemistry: 19% **On-Therapy Post-Progression Resource Use** Physician visit: 0% Complete blood count test: 39% Biochemistry: 33% **Off-Therapy Post-Progression Resource Use** Physician visit: 8% Complete blood count test: 39% Biochemistry: 33%	[redacted]	[redacted]	121,209
20-year time horizon	20-year time horizon captures the majority of differences between costs and outcomes	[redacted]	[redacted]	126,312
1.5% effectiveness discount rate	Outcomes are discounted at 1.5% annual rate (and costs discounted at 3.5%)	[redacted]	[redacted]	111,055

1.5% cost discount rate	Costs are discounted at 1.5% annual rate (and outcomes discounted at 3.5%)	[redacted]	[redacted]	133,724
1.5% effectiveness and cost discount rates	Costs and outcomes are discounted at a 1.5% annual rate	[redacted]	[redacted]	119,050
EQ-5D-5L utilities	**Progression-Free On- and Off-Treatment utility** IsaPd: [redacted] Pd: [redacted] DARA: [redacted] **Post-progression On- and Off-Treatment utility** IsaPd: [redacted] Pd: [redacted] DARA: [redacted] **Terminal decrement in utility** IsaPd: [redacted] Pd: [redacted] DARA: [redacted]	[redacted]	[redacted]	124,403
Isa dosing based on ICARIA weight distribution	Isatuximab discount: [redacted]. Based on separate calculations examining the cost difference when weight distribution vs. mean weight was used in isatuximab costing, it was found that using a weight distribution resulted in a [redacted] reduction in overall cost of isatuximab. This was implemented as a secondary discount after accounting for the PAS discount.	[redacted]	[redacted]	124,034
Pomalidomide and dexamethasone RDI in IsaPd combination based on RWE	Pomalidomide RDI: [redacted] Dexamethasone RDI: [redacted]	[redacted]	[redacted]	124,631
IsaPd SACT TTD/PFS/PFS On-Tx: RCS Weibull	IsaPd SACT TTD distribution set to RCS Weibull vs Base case: Lognormal	[redacted]	[redacted]	103,265
Pd SACT TTD/PFS/PFS-On-Tx: Lognormal	Pd SACT TTD/PFS/PFS-On-Tx set to Lognormal vs Base case: Log-Logistic	[redacted]	[redacted]	126,757
Pd SACT TTD/PFS/PFS-On-Tx: RCS Log-Logistic	Pd SACT TTD/PFS/PFS-On-Tx set to RCS Log-Logistic vs Base case: Log-Logistic	[redacted]	[redacted]	119,674
Isa administered as subcutaneous	Isatuximab administered as a subcutaneous formulation	[redacted]	[redacted]	120,030

	• Dose/administration: 1400 mg/day • RDI: [redacted] Adverse event rates derived from Quach 2022 study			
IsaPd SACT OS: RCS Lognormal 2k, Pd SACT OS: RCS Weibull	IsaPd SACT OS distribution: RCS Lognormal 2k (mid-range survival chosen by clinical experts) Pd SACT OS: RCS Weibull (upper range survival chosen by clinical experts)	[redacted]	[redacted]	138,463
IsaPd SACT OS: RCS Lognormal 2k, Pd SACT OS: Weibull	IsaPd SACT OS distribution: RCS Lognormal 2k (mid-range survival chosen by clinical experts) Pd SACT OS distribution: Weibull (lower range survival chosen by clinical experts)	[redacted]	[redacted]	137,691
IsaPd SACT OS: Log-Logistic, Pd SACT OS: RCS Weibull	IsaPd SACT OS distribution: Log-Logistic (upper-range survival chosen by clinical experts, 2nd best fit) Pd SACT OS distribution: RCS Weibull (lower range survival chosen by clinical experts)	[redacted]	[redacted]	132,186
IsaPd SACT OS: Log-Logistic, Pd SACT OS: Weibull	IsaPd SACT OS distribution: Log-Logistic (upper-range survival chosen by clinical experts, 2nd best fit) Pd SACT OS distribution: Weibull (lower range survival chosen by clinical experts)	[redacted]	[redacted]	131,667

Abbreviations: BSA, body surface area; DARA, daratumumab; EQ-5D-5L, EuroQol five dimension five level; ICER, incremental cost-effectiveness ratio; Isa, isatuximab; IsaPd, isatuximab + Pd; k, knot; NICE, National Institute for Health and Care Excellence; OS, overall survival; PAS, patient access scheme; Pd, pomalidomide + dexamethasone; PFS, progression free survival; QALY, quality adjusted life years; RCS, restricted cube spline; RDI, relative dosing intensity; RWE, real world evidence; SACT, systemic anti-cancer therapy; TTD, time to discontinuation; Tx, treatment

2.4.3.2 *Probabilistic scenario analysis*

Select scenario analyses were also tested probabilistically, in which probabilistic model results are generated for a particular set of parameter estimates or assumptions (Table 20). The results are generated by running the probabilistic analysis, and assumptions regarding parameter sampling for each variable can be varied. The results consider the applicability of the PAS for isatuximab only, all other therapies are considered at list price.

Table 20. Scenario analysis (Probabilistic): IsaPd SACT vs Pd SACT

Scenario name	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case (probabilistic)	[redacted]	[redacted]	125,932
EQ-5D-5L utilities	[redacted]	[redacted]	125,497
Isa dosing based on ICARIA weight distribution	[redacted]	[redacted]	125,216
IsaPd pomalidomide and dexamethasone RDI based on RWE	[redacted]	[redacted]	125,932
IsaPd SACT OS: RCS Lognormal 2k, Pd SACT OS: RCS Weibull	[redacted]	[redacted]	138,862
IsaPd SACT OS: RCS Lognormal 2k, Pd SACT OS: Weibull	[redacted]	[redacted]	137,709
IsaPd SACT OS: Log-Logistic, Pd SACT OS: RCS Weibull	[redacted]	[redacted]	133,775
IsaPd SACT OS: Log-Logistic, Pd SACT OS: Weibull	[redacted]	[redacted]	132,865
IsaPd TTD (RCS Weibull)	[redacted]	[redacted]	105,239

Abbreviations: EQ-5D-5L, EuroQol five dimension five level; ICER, incremental cost-effectiveness ratio; Isa, isatuximab; IsaPd, isatuximab + Pd; k, knot; OS, overall survival; Pd, pomalidomide + dexamethasone; QALYs, quality adjusted life years; RCS, restricted cube spline; RDI, relative dosing intensity; RWE, real world evidence; SACT, systemic anti-cancer therapy; TTD, time to discontinuation.

2.5 Severity

Sanofi continue to maintain that IsaPd should be assessed at a cost-effectiveness threshold of £50,000/QALY, in line with the original appraisal, the expectation on entry to the CDF as well as the criteria applied at HTA recommendation for other regimens at 4th line.

The updated base case cost-effectiveness analysis using the Pd SACT data suggest that the 1.2 multiplier can now be applied to QALY gains when utilising the SACT vs SACT comparison for IsaPd and Pd. This brings the overall evidence in line with the observed QALY shortfall when using the DARA SACT data and is more reasonable compared to QALY shortfall that was suggested when using Pd data from ICARIA-MM in the previous base case analysis.

Using the updated age in the model (71 years), the general population would have on average 8.67 QALYs remaining. The new company base case estimates that patients in the Pd arm would accrue [redacted] QALYs compared with resulting in an absolute QALY shortfall of [redacted] and proportional QALY shortfall of [redacted], allowing the application of a 1.2 severity modifier for the comparison of IsaPd vs Pd (Table 21). The total LYG of [redacted] (<2 years) in the Pd arm also supports that IsaPd continues to meet the EoL threshold when the considering Pd as the relevant comparator and data from SACT is used.

Results applying [redacted], estimated confidential discounts as well as consideration of non-reference case analyses are provided in **Error! Reference source not found.**, Table 41 to Table 43 and results in improved ICERs.

Table 21. Base-case results (deterministic) vs Pd SACT with 1.2 severity modifier applied

Intervention	Total costs (£)	Total LYG	Total QALYs (weighted)	Inc. costs (£)	Inc. LYG	Inc. QALYs (weighted)	ICER (£/QALY)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	103,953

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + Pd; LYG, life years gained; Pd, pomalidomide + dexamethasone; QALYs, quality adjusted life years; SACT, systemic anti-cancer therapy; vs, versus.

2.6 Interpretation and impact of revised analysis for the cost-effectiveness of IsaPd vs Pd

Ongoing clinical expert feedback supports that despite availability of daratumumab monotherapy, Pd is the standard of care therapy choice should IsaPd not be available in the pathway and hence continues to be the most relevant comparator. The original company submission utilised efficacy data for IsaPd and Pd directly from the ICARIA-MM trial. Whilst the trial data contributed evidence for a clear benefit in PFS for IsaPd vs Pd, the use of daratumumab post-progression on the Pd and IsaPd arm did not reflect UK practice which was likely to confound the OS estimate and potentially underestimate the treatment effect of IsaPd on overall survival.

SACT data provides valuable RWE pertaining to the clinical effectiveness and observed outcomes of prescribed therapies. Whilst previously, SACT data for IsaPd was available from the CDF, data for Pd from SACT were notably absent. This updated analysis leverages RWE from England for both Pd and IsaPd, sourced from the SACT database. This methodology provides highly relevant evidence for decision-making, drawing from the same foundational source (NCRAS-SACT) and accurately reflecting clinical practices in England.

While acknowledging the simplicity of the comparison, it's important to note that rwPFS for Pd generally aligns with findings from the ICARIA-MM trial and MM-003 (Pd registration trial informing TA427 and TA783). Conversely, the overall survival (OS) estimate, influenced significantly by subsequent therapies reflective of clinical practice, understandably demonstrates less favourable outcomes compared to trial evidence for Pd. This trend is consistent across most RWE observed to date, as trial outcomes tend to be more favourable due to stringent entry criteria, whereas clinical practice involves a more heterogeneous patient population receiving the same treatment.

Moreover, the characteristics of patients receiving 4th line therapy in the SACT study (encompassing the population that received Pd in SACT) were similar to those contributing to the SACT analysis for IsaPd. This similarity lends strength and confidence to the use of this evidence as a basis for decision-making.

The updated base case analysis presented in this addendum continues to align with the NICE reference case and suggests an improvement in the cost-effectiveness of IsaPd compared to Pd utilising the real-world evidence available from a reputed data source for both therapies in England.

The base case analysis utilises a survival assumption for IsaPd that best fits the data period and is deemed plausible by clinical experts, in the absence of longer-term data. The survival curve chosen for Pd aligns to the EAG's preference for using the best fitting distribution for the comparator treatment, although clinical feedback pointed to worse survival expectations with Pd. Testing these alternative assumptions on Pd survival improved the ICER in favour of IsaPd. The cost effectiveness can improve further when confidential discounts for comparator, subsequent therapies, and [redacted] are considered (**Error! Reference source not found.**).

As described previously, the loss of the end of life (EoL) threshold (cost-effectiveness threshold of up to £50,000/QALY) due to the change in NICE methods and processes during the period in which IsaPd was accessible in the CDF is detrimental to the current appraisal. The base case using the most favourable survival assumptions for Pd continue to demonstrate total life years with Pd treatment to be <2 years and that treatment with IsaPd extends life by more than six months. Therefore, real-world evidence from Pd SACT supports the continued use of the EoL threshold in this re-appraisal.

The Pd SACT evidence also demonstrates a proportional QALY shortfall of [redacted], allowing the application of a 1.2 severity modifier for the comparison of IsaPd vs Pd. The company are aware that the uptake of severity modifiers since the publication of the new NICE manual has not been as high as was initially anticipated. This is therefore unlikely to have been an opportunity cost-neutral change to the NICE methods as was expected. We strongly feel that there is a case for IsaPd to be assessed at the same threshold (£50,000/QALY) as it was on entry into the CDF, and in line with other treatments already recommended for MM, particularly given the challenges of demonstrating cost-effectiveness for combination treatments.

Non-reference case analyses such as removing the cost of likely non-cost-effective background care (Pd) and considering patent expiry of pomalidomide (expected in Q2 2024) have also been presented. These provide informative evidence to the NICE committee and suggests that if the exceptionalities of this appraisal are considered, IsaPd could be deemed a cost-effective use of NHS resources at the £50,000/QALY threshold (once other discounts and [redacted] have been accounted for).

We believe that the evidence presented in this addendum provides strong support to the continued use of IsaPd as the standard of care for patients with RRMM and demonstrates that if the committee are able to apply flexibility in its decision making, IsaPd can be considered cost-effective and patients in England can continue to access an effective, triplet combination regimen that continues to address an unmet need at 4th line.

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Appendix A. Sanofi NCRAS study – detailed description

A.1 Detailed methods

A.1.1 Research questions and objectives

The study objectives were as follows:

1. Describe the following patient demographic and clinical characteristics at MM diagnosis and, where available, at the initiation of each LoT for all eligible MM patients overall:
    a. Age at diagnosis and at initiation of 1st, 2nd, 3rd, 4th line (if available)
    b. Sex
    c. Weight at initiation of 1st, 2nd, 3rd, 4th line (if available)
    d. Year of diagnosis
    e. Ethnicity
    f. Charlson Comorbidity Index (CCI) at diagnosis
    g. ECOG Performance status at diagnosis and at initiation of 1st, 2nd, 3rd, 4th line (if available)
    h. Stage of disease at diagnosis
    i. Tumour morphology code (ICD-O-2)
    j. Follow-up time from diagnosis and from initiation of 1st, 2nd, 3rd, 4th line (if available)
    k. Record of a SCT post-diagnosis
    l. Total LoTs received following MM diagnosis

    Additionally, for patients receiving 1st, describe the following characteristics at the initiation of 1st line, overall and stratified by transplant status (received in any line):
    m. Age at initiation of 1st line
    n. Weight at initiation of 1st line
    o. ECOG performance status at initiation of 1st line
    p. Follow-up time from initiation of 1st line.

    Patients receiving drugs through the CDF will be included as a distinct sub-population when describing demographic and clinical characteristics at diagnosis if there is a sufficient sample size (exploratory objective).

2. Describe the treatment pathway and patterns for patients with newly diagnosed multiple myeloma, including:
    a. Time from diagnosis to treatment initiation by LoT

3. Describe the distribution of SACT treatments (mono/combo regimen level) received after MM diagnosis among patients with at least one SACT record

overall and stratified by LoT, and stratified by transplant status (received in any LoT) for patients receiving 1st line.

4. Describe the longitudinal sequencing of SACT treatments received among patients with MM and at least one SACT record, overall and stratified by transplant status (received in any LoT). Additionally, describe the longitudinal sequencing of SACT regimens of interest received at 1st line, overall and stratified by transplant status (received in any LoT).

5. Describe duration of treatment for patients with MM and at least one SACT record by LoT, including:
    a. Treatment duration (TD, duration of LoT) overall
    b. Treatment duration for the most commonly occurring SACT regimen groups
    c. TTNT (time to next LoT) overall
    d. Time to next treatment for the most commonly occurring SACT regimen groups

6. Describe the survival outcomes PFS (proxied by TTNTD) and OS for the following patients with MM:
    a. Patients with at least one SACT record, assessed from the start of each LoT and stratified by:
        i. LoT
        ii. LoT and by the most commonly occurring SACT regimen groups
    b. Patients receiving 1st line, assessed from the start of 1st line and stratified by:
        i. Transplant status (received in any LoT)
        ii. Transplant status (received in any LoT) and by the most commonly occurring SACT regimen groups
        iii. Transplant status (received in 1st line only)
        iv. Transplant status (received in 1st line only) and by the most commonly occurring SACT regimen groups
        v. Transplant status (received in 1st line only) and by SACT regimens of interest
    c. Patients receiving SACT regimens of interest in any LoT, assessed from the start of the SACT regimen of interest and stratified by:
        i. SACT regimens of interest

7. Describe the following HCRU outcomes from diagnosis until death or loss to follow- up among patients with MM and at least one SACT record, overall and stratified by LoT and the most commonly occurring regimen groups:
    a. Number of hospital admissions from diagnosis
        i. Inpatient

ii. Outpatient

iii. Accidents and emergencies

b. Length of inpatient hospital stay

HCRU will be split into time periods from date of diagnosis and initiation of LoT.

Additionally, for patients receiving the SACT regimens of interest at 1st line, describe HCRU outcomes from diagnosis until death or loss to follow-up, stratified by SACT regimens of interest at 1st line.

A.1.2 Study time period

The overall Study Time Period was from 1 January 2014 to 31 August 2021, with slight variations in the periods of patient identification, treatment pathway, and survival ascertainment:

- **Patient Identification Time Period:** The period to identify incident MM cancer patients was from 1 January 2014 to 31 December 2019, as this was the last date of data availability in the COSD within CAS at the time of data extraction.

- **Treatment Pathway Time Period:** The period to evaluate treatment pathways is from 1 January 2014 to 31 May 2021, as this was the last date of data availability in the SACT dataset within CAS at the time of data extraction.

- **Survival Ascertainment Time Period:** The period to ascertain vital status of study patients is from 1 January 2014 to 31 August 2021, as this was the last date for which mortality data from the Office for National Statistics (ONS) are updated within CAS at the time of data extraction.

The overall **HCRU Time Period** was from 1 January 2014 to 31 March 2021, as this was the last date of data availability in the linked HES database at the time of data extraction. Accident & Emergency (A&E) data was only available to 31 March 2020.

A.1.2.1. *Index dates*

Several index dates relevant to each patient's period of follow-up and contribution to the analysis were used (Table 22).

Table 22: Specific dates of interest

Diagnosis index date	Date of the 1st recorded diagnosis of MM within the patient identification time period
Start of 1st treatment	Start of the 1st/Nth LoT
Start of 2nd/Nth	Start of the 2nd/Nth LoT
End of 1st/Nth	End date of the 1st/Nth LoT
Date of SCT	Date of the 1st recorded SCT following the diagnosis index date

Abbreviations: HES, Hospital Episodes Statistics; LoT, line of treatment; MM, multiple myeloma; SCT, stem cell transplant.

A.1.2.2. *Follow-up and censoring*

Patients were monitored from their Diagnosis Index Date until one of the following occurred:

- Date of death
- Date of the most recent 'alive' status in the COSD
- Date of loss to follow-up
- End of data availability.

The patient's vital status, determining whether they are alive, deceased, or lost to follow-up within the CAS database, is derived from COSD data. Mortality information is regularly updated in CAS, using data from the UK ONS, and checked every three months to confirm vital status.

SACT follow-up time is the duration from the Treatment Index Date (inclusive) to the point of exiting the cohort (exclusive).

A.1.3 Data sources

NHS Digital collects, stores, and analyses data through the NDRS. An important component of NDRS is the NCRAS, which maintains the datasets that comprises CAS. A summary and description of the data sources informing this study are provided in Table 23.

Table 23: Description of data sources

Data source	Description
CAS	NHS Digital collects data on nearly all cancer patients in England, maintained in a database called the CAS. The CAS comprises the well-known SACT and COSD datasets, which contains detailed patient-level information about tumours and mortality, and other linked datasets.
SACT	The SACT dataset captures nearly all treatments for cancer patients in the hospital inpatient, outpatient, and community settings. These include traditional chemotherapy drugs (infusion/injection/orals), biologics, immunotherapy, hormones, and drugs administered as part of clinical trials; however, recording of other treatments (e.g. steroids) is not complete and often at the discretion of the treating clinician. Information relating to patient performance status at the start of treatment (as an indication of general wellbeing and activities of daily living) may also be available in the SACT database. At the time of data extraction, SACT data were complete up to 31 May 2021. No further data were available and this was the last data availability time frame.
COSD	The COSD dataset has been the national standard for reporting cancer in the NHS in England since January 2013, providing unparalleled clinical detail on patients diagnosed with cancer, including age, sex, ethnicity, performance status at diagnosis, tumour morphology, histology, staging, grade, surgery, and patient date of death. The time lag on data in COSD is more significant than SACT. At the time of data extraction, COSD data were complete to the 31 December 2019 and vital status (updated through ONS) was complete up to 31 August 2021.
HES	The HES dataset is produced by the HSCIC, a non-departmental government body that houses and safeguards UK healthcare data. It captures reimbursement data as well as data on admissions, outpatient appointments and A&E department attendances, and higher cost diagnostic imaging at NHS hospitals in England. Data are collected during the patient's time at hospital (either in an outpatient, emergency department or inpatient care setting), resulting in over 125 million records per year, including information for all hospital-based activity in England. HES data was used in this study to identify HCRU and hematopoietic SCT procedures. At the time of data extraction, HES data was complete up to 31 March 2021, although A&E data was only available until 31 March 2020. Data from HES obtained in this study are not presented in this addendum as they do not contribute to any of the key outcomes of interest to the decision problem.

Abbreviations: A&E, Accident and Emergency; CAS, Cancer Analysis System; COSD, Cancer Outcomes and Services; HCRU, healthcare resource use; HES, Hospital Episode Statistics; HSCIC, Health and Social Care Information Centre; NHS, National Health Service; ONS, Office for National Statistics; SACT, Systemic Anti-Cancer Therapy; SCT, stem cell transplant; UK, United Kingdom/

A.1.4 Data linkage and data pooling

Data linkage between CAS and HES via patient-unique identification numbers was done by NHS Digital. This provided comprehensive coverage of clinical and demographic characteristics, SACT treatments, outcomes, and hospitalisation records among cancer patients, thereby providing a complete picture of the patient pathway for patients with MM in England.

A.1.4.1. *CDF-funded therapies*

The therapies on the CDF register as of 24 March 2022, are listed in Table 2. In this analysis, patients who received any therapy from the CDF list at the time of analysis were included in demographic and clinical descriptions as an exploratory objective; however, these patients were by default excluded from analysis for all other study objectives to avoid

compromising the NICE appraisal process. The data for these patients are therefore not presented here.

Table 24: Treatments for MM on the CDF register at the time of study data extraction

Blueteq reference	Drug
DAR2_v1.5	Daratumumab + bortezomib + dexamethasone for 2nd line For 3rd line, if 2nd line consisted of ixazomib + lenalidomide + dexamethasone
ISA1_v1.1	Isatuximab + pomalidomide + dexamethasone for 4th line
IXA1_v1.5	Ixazomib + lenalidomide + dexamethasone for 3rd/4th line

Abbreviations: CDF, Cancer Drugs Fund; MM, multiple myeloma.

A.1.5 Data collection

A.1.5.1. *Variables relevant to the decision problem*

Table 25 provides a summary of all patient populations of interest, index dates, variables to be reported, and stratifications required for each study objective. Patients receiving drugs through the CDF are excluded from all patient populations unless otherwise specified.

Table 25: Summary of variable reported by study objective

Objective	Population	Index Date	Variables	Stratification (1)	Stratification (2)
1. Demographic and clinical characteristics	All patients with MM	Diagnosis	Age Sex Year of diagnosis Ethnicity CCI ECOG score Stage Morphology Follow-up time SCT post-diagnosis Total LoTs received	None (overall)	–
		Start of LoT	Age Weight ECOG score Follow-up time	None (overall)	–
	Patients receiving 1st line	Start of 1st line	Age Weight ECOG score Follow-up time	SCT (any LoT)	–
	All patients receiving CDF drugs *(exploratory)*	Diagnosis	*If available:* Age Sex Year of diagnosis Ethnicity CCI ECOG score Stage Morphology Follow-up time	None (overall)	–
	All patients with MM (including patients receiving CDF drugs) *(exploratory)*				

Objective	Population	Index Date	Variables	Stratification (1)	Stratification (2)
			SCT post-diagnosis		
2. Time to treatment initiation	SACT-treated patients	Diagnosis	Time to initiation of LoT	LoT	–
3. Distribution of SACT treatments	SACT-treated patients	Start of 1st line	SACT (group-level and regimen- level)	LoT	–
	Patients receiving 1st line	Start of 1st line	SACT (group-level and regimen- level)	SCT (any LoT)	–
4. Longitudinal SACT sequencing	SACT-treated patients	Start of 1st line	Sequence of grouped SACT regimens (1st – 4th line)	None (overall)	–
				SCT (any LoT)	
	Patients receiving SACT regimens of interest in 1st line	Start of 1st line	Sequence of SACT regimens of interest (1st – 4th line)	None (overall)	–
				CT (any LoT)	
5. Duration of treatment	SACT-treated patients	Start of LoT	TD TTNT	LoT	–
				LoT	SACT regimen groups
6. Survival outcomes	SACT-treated patients	Start of LoT	PFS (proxied by TTNTD) OS	LoT	–
				LoT	SACT regimen groups by top 5 most common
	Patients receiving 1st line	Start of 1st line	PFS (proxied by TTNTD) OS	SCT (any LoT)	–
				SCT (any LoT)	SACT regimen groups
				SCT (1st line)	–
				SCT (1st line)	SACT regimen groups
				SCT (1st line)	SACT regimens of interest
	Patients receiving SACT regimens of interest (any LoT)	Start of SACT regimen of interest	PFS (proxied by TTNTD) OS	SACT regimens of interest	–

Objective	Population	Index Date	Variables	Stratification (1)	Stratification (2)
7. HCRU outcomes	SACT-treated patients	Diagnosis	Number of hospital admissions Length of inpatient stay	None (overall)	
				LoT	SACT regimen groups
	Patients receiving SACT regimens of interest (1st line only)	Diagnosis	Number of hospital admissions Length of inpatient stay	SACT regimens of interest (1st line)	

Abbreviations: CCI, Charlson Comorbidity Index; CDF, Cancer Drugs Fund; ECOG, Eastern Cooperative Oncology Group; HCRU, healthcare resource use; LoT, line of therapy; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival; SACT, systemic anti-cancer therapy; SCT, stem cell transplant; TD, treatment duration; TTD, time to treatment discontinuation; TTNTD, time to next treatment or death.

Baseline variables

Patient demographic and clinical characteristics were captured from the relevant database for each variable (CAS [COSD and SACT] and HES) and reported for all eligible patients, for the overall cohort (i.e. all eligible patients excluding CDF), for the SACT-treated cohort, and for the CDF cohort.

A.1.6 Line of therapy algorithm

A.1.6.1. *Rules specific for patients with an SCT record before any SACT records*

The following rules were applied for patients with an SCT record before any SACT records:

[redacted]

A.1.6.2. *Rules for identifying each LoT*

The following rules were applied for identifying each LoT:

[redacted]

[redacted]

For all regimens:

[redacted]

A.1.6.3. *Regimen end dates- Additional information*

Table 26. Common SACT regimens for the treatment of MM, including maximum cycle length for regimen end date calculation

Regimen	SACT agents included	Max Cycle length (days)	
		Clinical expert	NHS/NICE Guidelines (7, 8)
VTd	Bortezomib (Velcade) + Thalidomide + dexamethasone*	28-35	28
Vd	Bortezomib + dexamethasone*	21-35	21
VCd	Bortezomib + Cyclophosphamide + dexamethasone*	21-35	28
D-VTd	Daratumumab + Bortezomib + Thalidomide + dexamethasone*	–	28
CTd	Cyclophosphamide + Thalidomide + dexamethasone*	21-28	21
CTda	Cyclophosphamide + Thalidomide + attenuated dexamethasone*	21-28	28
Td	Thalidomide + dexamethasone*		daily
VMp	Bortezomib + Melphalan + prednisone*	35	35
MpT	Melphalan + Thalidomide + prednisone*	28	28
Rd	Lenalidomide (Revlimid) + dexamethasone*	28	28
Vd	Bortezomib (Velcade) + dexamethasone*	21-35	21
DVd *(CDF)*	Daratumumab + Bortezomib + dexamethasone*	21-28	28
IxaRd *(CDF)*	Izaxomib + Lenalidomide + dexamethasone*	28	28
Pd	Pomalidomide + dexamethasone*	28	28
Kd	Carfilzomib (Kyprolis) +	28	28

	dexamethasone*		
PanVd	Panobinostat + Bortezomib + dexamethasone*	21-28	28
dTPACE	dexamethasone + Thalidomide + Cisplatin + Doxorubicin (Adriamycin) + Cyclophosphamide + Etoposide	–	4+28 28 days & blood count recovery
VdTPACE	Bortezomib + dexamethasone + Thalidomide + Cisplatin + Doxorubicin + Cyclophosphamide + Etoposide	–	28
DARA	Daratumumab	28	28
KRd	Carfilzomib + Lenalidomide + dexamethasone*	28	28
IsaPd *(CDF)*	Isatuximab + Pomalidomide + dexamethasone*	28	28
Benda	Bendamustine	–	28
*Corticosteroids can be recorded as dexamethasone, prednisone, methylprednisone, methylprednisolone, and prednisolone		–	
Bortezomib Alkylating agent corticosteroid		–	28
Thalidomide Alkylating agent corticosteroid		–	42
Alkylating agents: Altretamine **Bendamustine** Busulfan Carboplatin Carmustine Chlorambucil Cisplatin **Cyclophosphamide** Dacarbazine Ifosfamide Lomustine Mechlorethamine **Melphalan** Oxaliplatin Temozolomide Thiotepa Trabectedin			

SCT ineligible SCT eligible

Abbreviations: CDF, Cancer Drugs Fund; M, multiple myeloma; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SACT, systemic anti-cancer therapy; SCT, stem cell transplant.

Table 27: Supporting agents in BENCHMARK_GROUP

BENCHMARK_GROUP	Indication
Zoledronic acid	Used to treat bone disease, reduce future skeletal related events, and treat hypercalcaemia
Denosumab	Used to treat bone disease, reduce future skeletal related events, and treat hypercalcaemia
Disodium pamidronate	Used to treat bone disease, reduce future skeletal related events, and treat hypercalcaemia
Intrathecal methotrexate	CNS prophylaxis
Sodium clodronate	Used to treat bone disease, reduce future skeletal related events, and treat hypercalcaemia
Zoledronic acid	Used to treat bone disease, reduce future skeletal related events, and treat hypercalcaemia

A.1.7 Data management plan and quality assurance

Data management for this study was conducted according to standard IQVIA (vendor conducting the study on behalf of Sanofi) processes, taking into consideration the data governance imposed on CAS data including any plans to handle the data outside of the institution or country of origin. IQVIA adhered to all local and regional laws on data protection and privacy.

To ensure the quality and integrity of research, this study was conducted under the guidelines for good pharmacoepidemiology practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki and its amendments, and applicable national guidelines, laws, and regulations.

A.2 Detailed results

A.2.1 Participants

Demographic and clinical characteristics at diagnosis for patients in the overall cohort (i.e. all eligible patients with MM who had not received a drug that was on the CDF register at the time of analysis, N=20,240) are provided in Table 28.

Table 28: Demographic and clinical characteristics available at diagnosis for patients in the overall cohort

Characteristic	N	%
Age at diagnosis		
N	20,240	100.0%
Mean (SD)	71.8 (12.3)	–
Median (Q1 – Q3)	73.0 (64.0 – 81.0)	–
Percentile 5^{th} – 95^{th}	50.0 – 89.0	–
Sex at diagnosis		
Male	11,338	56.0%
Female	8,902	44.0%
CCI at diagnosis		
0*	10,147	50.1%

Characteristic	N	%
1	4,205	20.8%
2	2,483	12.3%
3	1,610	8.0%
4+	1,795	8.9%
ECOG score at diagnosis		
0	3,331	16.5%
1	2,939	14.5%
2	1,233	6.1%
3	682	3.4%
4	203	1.0%
Missing/Unknown	11,852	58.6%
Staging at diagnosis (ISS)		
I	2,113	10.4%
II	1,973	9.8%
III	1,944	9.6%
Missing/Unknown	14,210	70.2%
Follow-up time from diagnosis (months)		
N	20,240	100.0%
Mean (SD)	32.9 (24.7)	–
Median (Q1 – Q3)	29.5 (11.1 – 49.9)	–
Percentile 5^{th} – 95^{th}	0.6 – 79.7	–
SCT received during follow-up		
No	16,639	82.2%
Yes	3,601	17.8%
Total number of LoTs received during follow-up		
0	8,145	40.2%
1	6,990	34.5%
2	3,127	15.5%
3	1,196	5.9%
4	472	2.3%
5	200	1.0%
6+	110	0.5%

Abbreviations: CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; LoT, line of therapy; Q, quarter; SCT, stem cell transplant; SD, standard deviation.

The SACT treated cohort included patients with MM who received at least one SACT, and who had received (at any LoT) a drug which was not on the CDF list at the time of analysis (N=12,095). Of the SACT-treated cohort, 782 patients received 4 or more LoTs; demographic and clinical characteristics at initiation of 4^{th} line are provided in Table 6.

A.2.2 Treatment duration

Median treatment duration decreased at each LoT and was estimated to be 3.7 months (95% CI: 3.5, 4.3) for patients receiving 4th line (Table 8).

At 4th line, patients receiving an investigational drug in a trial setting had the longest median treatment duration (10.1 months, 95% CI: 5.1, not available [N/A]), compared with other common regimens (pomalidomide: 3.2 months, 95% CI: 2.7, 4.1; bortezomib + panobinostat: 3.5 months, 95% CI: 2.5, 5.3; daratumumab: 3.8 months, 95% CI: 3.3, 4.8; lenalidomide: 5.2 months, 95% CI: 3.7, 8.8) (Table 8).

Table 29: Median treatment duration for patients in the SACT-treated cohort, including for patients receiving the most common regimen groups at 4th line

Cohort	Median TD (95% CI)	Number of patients
Patients receiving 4th line	***3.7 (3.5, 4.3)***	***751***
Daratumumab	3.8 (3.3, 4.8)	236
Pomalidomide	3.2 (2.7, 4.1)	175
Lenalidomide	5.2 (3.7, 8.8)	70
Bortezomib + panobinostat	3.5 (2.5, 5.3)	69
Trial	10.1 (5.1, N/A)	29

Abbreviations: CI, confidence interval; N/A, not available; SACT, Systemic Anti-Cancer Therapy; TD, treatment duration.

A.2.3 Time to next treatment

Overall, TTNT decreased by an average of 29% at each LoT. Median TTNT was estimated to be 11.2 months (95% CI: 9.9, 13.2) for patients receiving 4th line. Median TTNT was estimated to be 8.4 months (95% CI: 7.1, 10.8) for patients receiving daratumumab to 25.7 months (95% CI 14.5, N/A) for patients receiving investigational drugs in a trial setting (Table 30).

Table 30: Median time to next treatment for patients in the SACT-treated cohort, including for patients receiving the most common regimen groups at 4th line

Cohort	Median TTNT (95% CI)	Number of patients
Patients receiving 4th line	***11.2 (9.9, 13.2)***	***751***
Daratumumab	8.4 (7.1, 10.8)	236
Pomalidomide	18.8 (12.9, N/A.)	175
Lenalidomide	19.9 (9.7, 35.5)	70
Bortezomib + panobinostat	9.4 (8.6, N/A.)	69
Trial	25.7 (14.5, N/A.)	29

Abbreviations: CI, confidence interval; N/A, not available; SACT, Systemic Anti-Cancer Therapy; TTNT, time to next treatment.

A.2.4 Time to next treatment or death

For patients receiving 4th line, median TTNTD was 5.6 months (95% CI: 4.8, 6.1) (Table 31). Median TTNTD ranged from 4.7 months (95% CI: 3.9, 6.0) with pomalidomide to 20.1 (95% CI 11.1, NA) with investigational drugs in clinical trials.

Table 31: Median time to next treatment or death for patients in the SACT-treated cohort, including for patients receiving the most common regimen groups at 4th line

Cohort	Median TTNTD (95% CI)	Number of patients
Patients receiving 4th line	***5.6 (4.8, 6.1)***	***751***
Daratumumab	5.5 (4.4, 6.6)	236
Pomalidomide	4.7 (3.9 – 6.0)	175
Lenalidomide	9.2 (6.2, 12.2)	70
Bortezomib + panobinostat	5.3 (3.8, 7.4)	69
Trial	20.1 (11.1, N/A.)	29

Abbreviations: CI, confidence interval; N/A, not available; SACT, Systemic Anti-Cancer Therapy; TTNTD, time to next treatment or death.

A.2.5 Overall survival

For patients receiving 4th line, median OS was 11.5 months (95% CI: 9.8, 13.4). In patients receiving investigational drugs through clinical trials, median OS was not reached. Median OS ranged from 6.3 months (95% CI: 4.6, 7.8) with pomalidomide to 21.2 months (95% CI: 11.4, 35.9) with lenalidomide.

Table 32: Median overall survival for patients in the SACT-treated cohort, including for patients receiving the most common regimen groups at 4th line

Cohort	Median OS (95% CI)	Number of patients
Patients receiving 4th line	***11.5 (9.8, 13.4)***	***751***
Daratumumab	15.4 (13.8, 19.9)	236
Pomalidomide	6.3 (4.6, 7.8)	175
Lenalidomide	21.2 (11.4, 35.9)	70
Bortezomib + panobinostat	8.0 (4.6, 11.6)	69
Trial	not reached	29

Abbreviations: CI, confidence interval; OS, overall survival; SACT, Systemic Anti-Cancer Therapy.

Appendix B. Pd data from other UK real-world evidence literature

Table 33: Included UK Pd studies in 4th line population: Summary study characteristics – details of funding, objective, trial design, location, trial date and outcomes

Abbreviated citation + reference (secondary/linked publications)	Funder	Objective	Trial design (Dates of study)	Inclusion criteria	Exclusion criteria	Country (Sites)	Outcomes
Miles, 2015 (4)	Not reported	To compare 'real-world' POM outcomes across four UK regional hospitals against data from the MM-003 trial	Retrospective study (not reported - 18 month period)	RRMM patients initiating pomalidomide	Not reported	UK (4)	OS; PFS; AEs
Wells, 2015 (5)	Not applicable	To determine whether real world data mirrors MM-003 clinical trial	Retrospective study (17 months - prior to January 2015)	RRMM patients of age ≥20 years who were treated with at least two previous regimens and had undergone treatment with the Pd regimen from February 2016 to March 2020	Patients without a history of regular follow-up and those with non-secretory MM	UK (5)	ORR; OS

Abbreviations: AEs, adverse events; DoR, duration of response; IsaPd, isatuximab plus pomalidomide plus dexamethasone; MM, multiple myeloma; NICE, National Institute for Health and Care Excellence; ORR, objective response rate; OS, overall survival; Pd, pomalidomide plus dexamethasone; PFS, progression free survival; PN, peripheral neuropathy; POM, pomalidomide; RRMM, relapsed refractory multiple myeloma; SPM, secondary primary malignancies; Tx, treatment; UK, United Kingdom; VTE, venous thromboembolism.

Table 34: Summary baseline characteristics RWE UK Pd studies in 4th line population

Abbreviated citation + Endnote ID	Treatment arm	Number of participants	Age [years] Median (range)	Gender, n (%) male	ECOG performance status, n (%)	Number of prior lines of therapy Median (range) or n (%)	Time since diagnosis median years (range)	ISS disease stage	Cytogenetic features n (%)
Miles, 2015 (4)	Pd	38	69 (51, 86)	NR	NR	3 (3, 7)	NR	NR	NR
Wells, 2015 (5)	Pd	32	68.0 (51, 86)	23 (72)	NR	3 (3,5)	NR	NR	NR

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; IsaPd, isatuximab plus pomalidomide plus dexamethasone; ISS, International Staging System; NR, not reported; Pd, pomalidomide plus dexamethasone; Tx, treatment.

Table 35: Summary PFS results RWE UK Pd studies in 4th line population

Abbreviated citation + Endnote ID	Median follow-up months (range)	Intervention	Outcome definition of PFS	N	PFS: KM % at 6 months (95% CI)	PFS: KM % at 12 months (95% CI)	PFS: Median [months] (95% CI)
Miles, 2015 (4)	NR	Pd	NR	38	NR	NR	3.4 (NR)

†Total cohort; ǂResponse evaluable Abbreviations: CI, confidence interval; IsaPd, isatuximab plus pomalidomide plus dexamethasone; KM, Kaplan-Meier; NR, not reported; Pd, pomalidomide plus dexamethasone; PFS, progression free survival

Table 36: Summary OS results RWE UK Pd studies in 4th line population

Abbreviated citation + Endnote ID	Median follow-up months (range)	Intervention	Outcome definition of overall survival	N	OS: KM % at 6 months	OS: KM % at 12 months	OS: Median [months] (95% CI)
Miles, 2015 (4)	NR	Pd	NR	38	NR	NR	10.9 (NR)
Wells, 2015 (5)	NR	Pd	NR	32	NR	NR	10.9 (NR)

†Total cohort; ǂResponse evaluable
Abbreviations: CI, confidence interval; IsaPd, isatuximab plus pomalidomide plus dexamethasone; KM, Kaplan-Meier; NR, not reported; OS, overall survival; Pd, pomalidomide plus dexamethasone

Appendix C. DataSAT

C.1 RWE Data Suitability Assessment Tool (DataSAT): summary overview

Data provenance: The analysis utilised data from NHS Digital's National Disease Registration Service, facilitating comprehensive insights into the pathways of newly diagnosed MM patients in England. Data, encompassing clinical and demographic details, SACT treatments, and outcomes, originated from CAS (COSD and SACT). Spanning from 1 January 2014 to 31 August 2021, the study identified incident MM cases using ICD-10 codes and applied exclusion criteria for specificity. Data preparation involved rigorous cleaning, and masking procedures were employed for privacy. Governance adhered to CAS standards, and IQVIA ensured quality management aligned with pharmacoepidemiology practices. The study's protocol and final report can be made available.

Data relevance: The analysis focused on adult patients newly diagnosed with MM in England from 1 January 2014 to 31 August 2021. The research spanned hospital inpatient, outpatient, and community settings, encompassing the entire treatment pathway from newly diagnosed to the 4th line or beyond. Key study elements, exposures, and outcomes were sufficiently documented, with TTNTD serving as a proxy for PFS. The follow-up period extended from the date of diagnosis and treatment initiation to the earliest of death, loss to follow-up, or the end of the treatment pathway period (31 May 2021). The sample size included 12,095 patients with valid SACT records, with subsets such as the SACT-treated cohort and those receiving four or more lines of therapy providing specific insights into outcomes.

Data quality: The study clearly defined and assessed key variables related to MM patients and treatment outcomes. For the patient population, identified through the ICD-10 code C90.00, registry data from medical records ensured accuracy, though some demographic and baseline details were incomplete. In measuring treatment duration, TTNT and TTNTD, the study relied on a robust algorithm, outlined in the protocol, due to the database's inability to directly capture treatment details. OS outcomes were accurately assessed using registry data, recognising the objective nature of death as an outcome. Emphasising accuracy, the study transparently acknowledged potential limitations, such as the reliance on algorithms for specific data elements.

Risk of bias: To mitigate selection bias at study entry, a target trial framework was implemented, clearly delineating inclusion and exclusion criteria. Although all MM patients in the CAS were eligible, the exclusion of individuals undergoing specific treatments introduced a moderated risk of bias. The study diligently tracked patients from diagnosis to various endpoints, actively addressing potential bias at study exit. Concerning confounding, the longitudinal analysis aimed to offer a comprehensive understanding of MM patients' characteristics and treatments. Data were reported as collected avoiding both imputation and prognostic factor stratification. Detection bias was acknowledged, particularly in outcomes TTNT and TTNTD, which relied on an algorithm due to inconsistent data recording. Rigorous algorithm development, guided by clinical input and data source-specific considerations, aimed to mitigate this risk. The risk of measurement error and misclassification

was deemed low for overall survival (OS) but moderate for TTNT and TTNTD. Missing data, particularly for baseline characteristics, were transparently reported. Reverse causation was not anticipated as a concern in this analysis. Overall, the study was judged to carry a low to moderate risk of bias.

C.2 RWE Data Suitability Assessment Tool (DataSAT)

Sanofi. Retrospective analysis of real-world multiple myeloma treatment sequencing, outcomes and resource use using Cancer Analysis System (CAS) database in England. 2023 (unpublished, data on file)

C.2.1 Research question

The detailed objectives of the primary study are provided in **Error! Reference source not found.**. In summary, the objectives of the primary study were to describe (overall, by line of therapy (LoT) [i.e. 1st line, 2nd line, 3rd line, 4th line], and transplant status, as necessary):

1. The patient demographic and clinical characteristics at MM diagnosis and, where available, at the initiation of each LoT.
2. The treatment pathway and patterns for patients with newly diagnosed MM.
3. The distribution of SACT treatments (mono/combo regimen level) received after MM diagnosis among patients with at least one SACT record.
4. The longitudinal sequencing of SACT treatments (1st line to 4th line) received among patients with MM and at least one SACT record.
5. The duration of treatment for patients with MM and at least one SACT record.
6. Treatment outcomes (PFS and OS).
7. HCRU outcomes from diagnosis until death or loss to follow-up among patients with MM and at least one SACT record.

The data presented in this addendum describes the following among 4th line patients;

1. Demographic and clinical characteristics of patients at initiation of any 4th line treatment.
2. Treatment duration and time to next treatment (TTNT) on pomalidomide.

3. Treatment outcomes on pomalidomide (time to next treatment or death [TTNTD] and overall survival [OS]).

C.2.2 Data provenance

Study	**Sanofi 2023: SACT Pd data**
Data sources	NHS Digital collects, stores, and analyses data through the National Disease Registration Service (NDRS). An important component of NDRS is the National Cancer Registration and Analysis Service (NCRAS), which maintains the datasets that comprises Cancer Analysis System (CAS).
Data linkage and data pooling	Data linkage between CAS and HES via patient-unique identification numbers was done by NHS Digital. This provided comprehensive coverage of clinical and demographic characteristics, Systemic Anti-Cancer Therapy (SACT) treatments, outcomes, and hospitalisation records among cancer patients, thereby providing a complete picture of the cancer patient pathway for patients with MM in England.
Type of data source	The CAS cancer registry comprises the well-known SACT and Cancer Outcomes and Services (COSD) datasets, which contains detailed patient-level information about tumours and mortality, and other linked datasets. • COSD has been the national standard for reporting cancer in the NHS in England since January 2013, providing clinical detail on patients diagnosed with cancer, including morphology, histology, staging, grade, surgery, and date of death • SACT dataset captures nearly all treatments for cancer patients in the hospital inpatient, outpatient, and community settings. This includes traditional chemotherapy drugs (infusion/injection/orals), biologics, immunotherapy, hormones and includes drugs for patients treated in clinical trials
Purpose of data collection	Clinical care
Data collection	Patient demographic and clinical characteristics were captured from the relevant database for each variable (CAS [COSD and SACT] and HES) and reported for all eligible patients, for the overall cohort (i.e., all eligible patients excluding CDF), for the SACT-treated cohort, and for the CDF cohort. Variables and operational definitions were clearly reported in the protocol
Care setting	Hospital = secondary care
Geographical setting	England
Population coverage	All adult patients newly diagnosed with MM during the patient identification time period were considered for inclusion in the study. Diagnoses of MM were identified using the 10th version of International Classification of Diseases (ICD-10) code: C90.00. Patients were eligible for inclusion in the study cohort if they met all the following criteria: Incident diagnosis of MM and aged ≥18 years at the date of incident MM diagnosis. Patients were excluded from the study cohort if they met any of the following criteria: • A record of SACT more than 30 days prior to the date of incident MM diagnosis.

Study	Sanofi 2023: SACT Pd data
	• A record of MM diagnosis prior to the Patient Identification Time Period. • A record of any other malignancy within the Study Time Period, except for non-melanoma skin cancer. Although the analysis presented was conducted to understand newly diagnosed MM patients in England, RWE from diagnosis to death/loss to follow-up was captured, and as a result, data relating to pomalidomide in later lines is also available
Time period of data	The overall Study Time Period was from 1 January 2014 to 31 August 2021, with slight variations in the periods of patient identification, treatment pathway, and survival ascertainment, as defined below: • **Patient Identification Time Period:** The period to identify incident MM cancer patients was from 1 January 2014 to 31 December 2019, as this was the last date of data availability in the Cancer Outcomes and Services Dataset (COSD) within CAS at the time of data extraction (Jan 2022, beginning of statistical analysis). • **Treatment Pathway Time Period:** The period to evaluate treatment pathways is from 1 January 2014 to 31 May 2021, as this was the last date of data availability in the SACT dataset within CAS at the time of data extraction (Jan 2022, beginning of statistical analysis). • **Survival Ascertainment Time Period:** The period to ascertain vital status of study patients is from 1 January 2014 to 31 August 2021, as this was the last date for which mortality data from the Office for National Statistics (ONS) are updated within CAS at the time of data extraction.
Data preparation	Data cleaning was carried out before the analyses were conducted to remove patients with missing variables in fields necessary for the analysis. In particular, the following incomplete records were removed: • Patients with a missing NHS number • Patients with missing age or sex at MM diagnosis • Patient with missing vital status information in the CAS database Additional data cleaning required for LoT development was clearly reported. Data cleaning was performed using R version 4.2.1 by the contracted vendor, IQVIA Ltd. To minimise risk of patient re-identification, Health Data Insights (HDI) perform masking such that a level of approximation is applied to all data values in CAS. By avoiding reporting the exact value of small patient numbers, iterative data requests are possible without violating governance standards. Masking was applied to all study outputs in line with the following rules set out by NHS Digital: • All small numbers 1-5 are replaced with *. • Minimum and maximum values are replaced with 5th and 95th percentile values.
Data governance	Data governance was as per the criteria imposed on CAS data
Data management plan and quality assurance methods	Data management for this study was conducted according to standard IQVIA processes, taking into consideration the data governance imposed on CAS data including any plans to handle the data outside of the institution or country of origin. IQVIA adhered to all local and regional laws on data protection and privacy.

Study	Sanofi 2023: SACT Pd data
	To ensure the quality and integrity of research, this study was conducted under the guidelines for good pharmacoepidemiology practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki and its amendments, and applicable national guidelines, laws, and regulations. At the study level, all aspects of the study (from protocol development to the reporting of results) were conducted within the framework of IQVIA's Quality Management System (QMS) and in accordance with the appropriate global policies and procedures, including: • RWI_OP_PM0020 "Record Management Guideline" • RWI_OP_PM0005 "Quality Control Strategy" policy • RWI_OP_BIOS0003 "Statistical Analysis Plan for Non-Interventional Retrospective Studies" • RWI_OP_PM0004 "Quality Control of Project Deliverables"
Other documents	Protocol and final report available (data on file)

Abbreviations: CAS, Cancer Analysis System; CDF, Cancer Drugs Fund; CAS, Cancer Analysis System; COSD, Cancer Outcomes and Services Dataset; HES, Hospital Episode Statistics; MM, multiple myeloma; ONS, Office for National Statistics; SACT, systemic anti-cancer therapy

C.2.3 Data quality

Study variable	Target concept	Operational definition	Quality dimension	How assessed	Assessment result
Population	Population	Adult patients newly diagnosed with MM. Diagnoses of MM were identified using the 10th version of International Classification of Diseases (ICD-10) code: C90.00	Accuracy	Registry (from medical records)	Medical records expected to be accurate. Some demographic and baseline characteristics are not anticipated to be complete
Outcome	Treatment duration	Treatment duration was defined as the time from the start date of a LoT to the earliest of the end date of a LoT/regimen or date of death	Accuracy	Registry (from medical records)	Medical records expected to be accurate. However, database does not directly capture LoTs or regimen end dates and was determined by an algorithm. The algorithm was

Study variable	Target concept	Operational definition	Quality dimension	How assessed	Assessment result
					described in the protocol
Outcome	Overall survival	OS was defined as time from initiation of each line of therapy until the date of death from any cause	Accuracy	Registry (from medical records)	Medical records expected to be accurate. Death objective outcome
Outcome	Time to next treatment	Time from the start date of each LoT (1st line - 4th line) to the start date of the next LoT	Accuracy	Registry (from medical records)	Medical records expected to be accurate. However, database does not directly capture LoTs or regimen end dates. The algorithm was described in the protocol
Outcome	Time to next treatment or death	Time from the start date of each LoT (1st line - 4th line) to the start date of the next LoT or death	Accuracy	Registry (from medical records)	Medical records expected to be accurate. However, database does not directly capture LoTs or regimen end dates. The algorithm was described in the protocol

Abbreviations: LoT, line of treatment

C.2.4 Data relevance

Study	Sanofi 2023: SACT Pd data
Population	Adult patients with newly diagnosed multiple myeloma. Although the analysis presented was conducted to understand newly diagnosed MM patients in England, RWE from diagnosis to death/loss to follow-up was captured, and as a result, data relating to pomalidomide in later lines is also available
Care setting	Hospital inpatient, outpatient, and community settings
Treatment pathway	Treatment was representative of clinical practice in England for patients with multiple myeloma from newly diagnosed to 4th line or more

Study	Sanofi 2023: SACT Pd data
Availability of key study elements	Sufficient data on exposures and outcomes are available. Outcomes were clearly defined. TTNTD was used as a proxy for PFS
Study period	1 January 2014 to 31 August 2021
Timing of measurements	No specific timing of measurement were made, as patients were followed through routine clinical practice. Outcome variables were clearly defined – time to event (OS, TTNT, TTNTD).
Follow up	The index date for patients was the date of diagnosis and start of line of treatment. The event (end date) was the earliest of date of death from any cause; date of loss to follow-up; or end of treatment pathway time period (31 May 2021)
Sample size	There were 12,095 patients with a valid SACT record (SACT-treated cohort), of which 211 (1.7%) had at least one line of therapy that contained only an SCT. Of the SACT-treated cohort available for analysis, 782 patients received 4 or more LoTs.

Abbreviations: Pd, pomalidomide and dexamethasone; PFS, progression-free survival; SACT, systemic anti-cancer therapy; SCT, stem cell transplant; TTNTD, time to next treatment or death.

C.2.5 Risk of bias

Type of bias	How bias was addressed or assessed
Selection bias at study entry	The risk of selection bias at study entry is considered moderate: Risk of selection bias at study entry was reduced by using a target trial framework defining inclusion and exclusion criteria for the population. All patients with MM recorded in CAS were eligible for inclusion in the study, subject to inclusion and exclusion criteria. However, due to the exclusion of patients with a record of having received (at any LoT) any treatment which was on the CDF register at the time of analysis, it was expected that the treatment patterns and outcomes observed for study participants would not be wholly representative of those for the more general cohort of SACT-treated patients. While there was no way to minimise the impact of this exclusion, the description of baseline characteristics for the CDF cohort was included as an exploratory objective in order to provide some contextualising information.
Selection bias at study exit	The risk of selection bias at study exit is considered moderate: Patients were followed from their Diagnosis Index Date to the earliest occurrence of one of the following: date of death; date of last vital status of patient determined to be 'alive' in COSD; date of loss to follow-up; and, end of data availability. Patient vital status is a derived variable in COSD that is used to determine whether a patient is alive, deceased, or lost to follow-up within the CAS database.
Addressing confounding	The risk of bias associated with addressing confounding is considered moderate. In the context of longitudinal studies, the potential for time-dependent covariates influenced by past treatments introduces the prospect of time-dependent confounding. This analysis tracks a cohort of newly diagnosed MM patients longitudinally, presenting a descriptive summary of patient characteristics and treatments administered from the first to the fourth line. Outcome variables encompass TTNT, TTNTD, and OS. TTNT and TTNTD are not directly observed but are derived through a predetermined algorithm. The analysis involves the summarization of data based on reported values, without imputations, and without stratification based on prognostic factors.

Type of bias	How bias was addressed or assessed
Detection bias	The risk of detection bias is considered moderate to high: Detection bias can occur in trials with differences in the way outcome information is collected (within study groups or between centres) or the way outcomes are verified. The outcome of mortality was not thought to be subject to detection bias. For outcomes TTNT or TTNTD, LoT was not directly captured, LoT or regimen end dates were not directly captured and classification was determined based on an algorithm. The algorithm was developed iteratively according to treatment guidance with expert clinical input, and data source-specific consideration. Due to the inconsistent recording of steroids and supportive agents in CAS, these did not impact on LoT progression rules and were not presented in study outputs. Regimen end dates were calculated based on median cycle duration, which was additionally limited based on available clinical guidelines.
Measurement error and misclassification	The risk of measurement error and misclassification is considered moderate. In the assessments of data quality, measurements seemed to correspond adequately to known clinical status. Errors identified by values outside standard normal ranges were few. LoT or regimen end dates were not directly captured and classification was determined based on an algorithm. The algorithm was developed iteratively according to treatment guidance with expert clinical input, and data source-specific consideration. Due to the inconsistent recording of steroids and supportive agents in CAS, these did not impact on LoT progression rules and were not presented in study outputs. Regimen end dates were calculated based on median cycle duration, which was additionally limited based on available clinical guidelines.
Missing data	The risk of measurement error and misclassification is considered moderate. Missing data for baseline characteristics with both ECOG PS and disease stage poorly recorded (missing or unknown). The number of participants with missing data for each variable was reported. Missing outcomes data and less frequent assessments in a real-world cohort compared to a clinical trial were recognised as a potential source of bias.
Reverse causation	Reverse causation is not expected to be a problem in this analysis.

Abbreviations: CAS, Cancer Analysis Registry; CDF, Cancer Drugs Fund; COSD, Cancer Outcomes and Services database; LoT, line of treatment; MM, multiple myeloma; TTNT, time to next treatment; TTNTD, time to next treatment or death

Appendix D. Pd SACT OS- Statistical fits and additional distributions

Figure 18: Fit statistics for parametric distributions to Pd OS from SACT

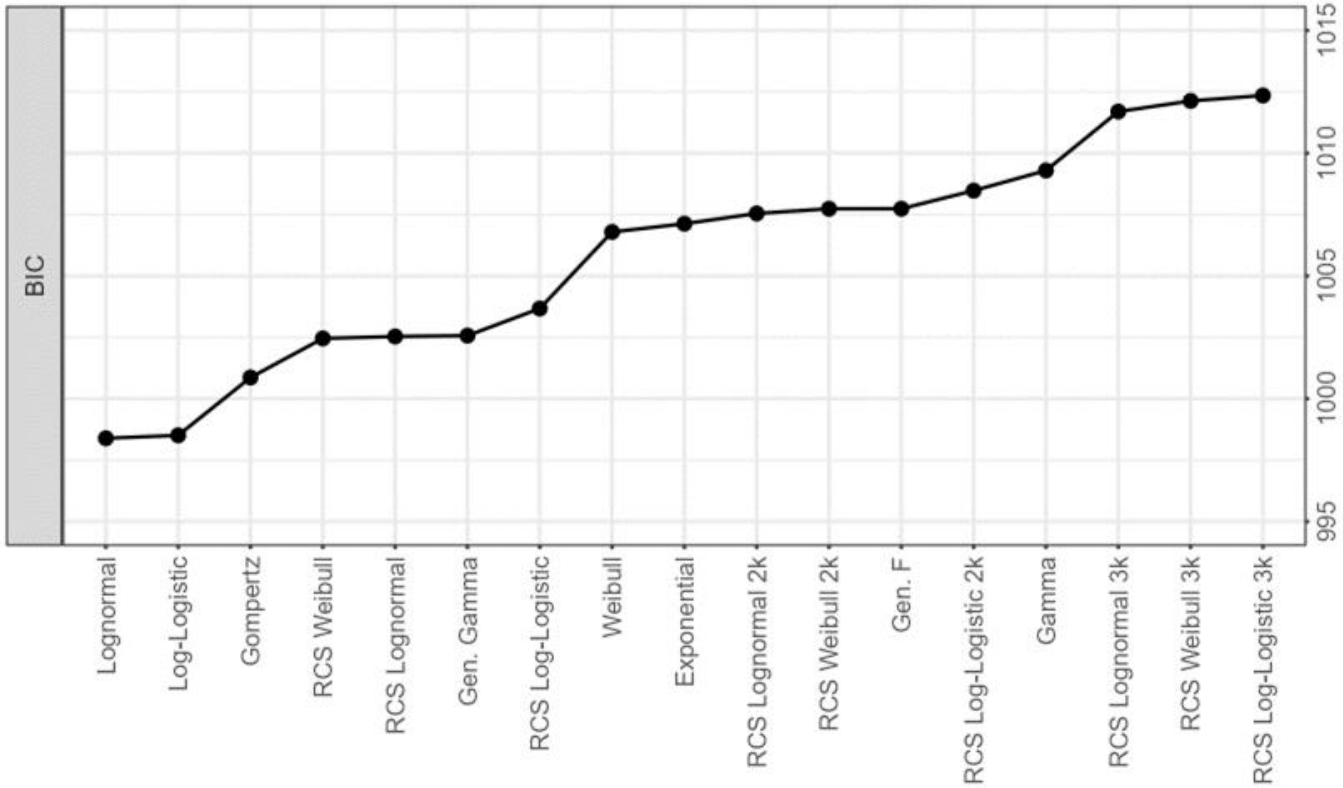
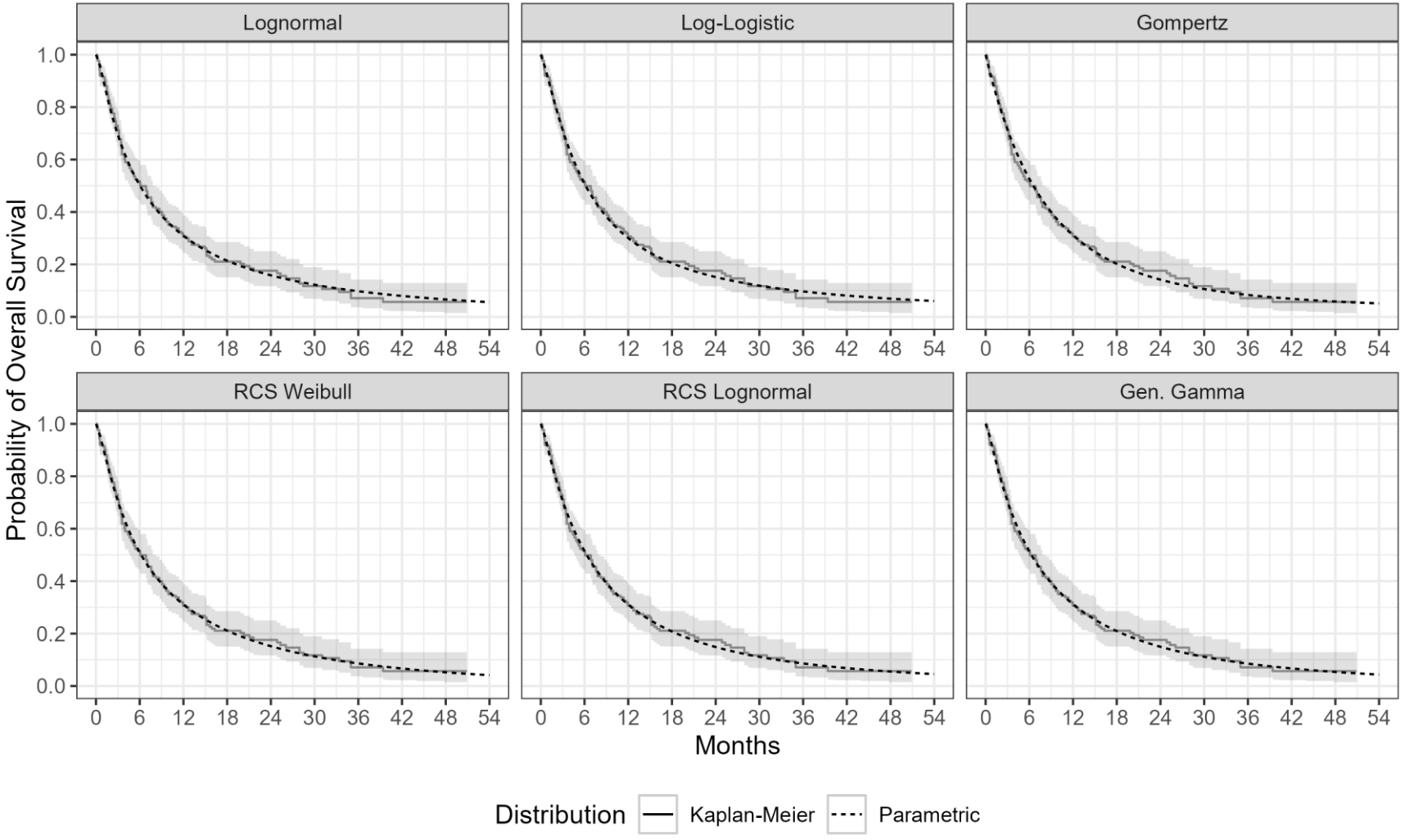
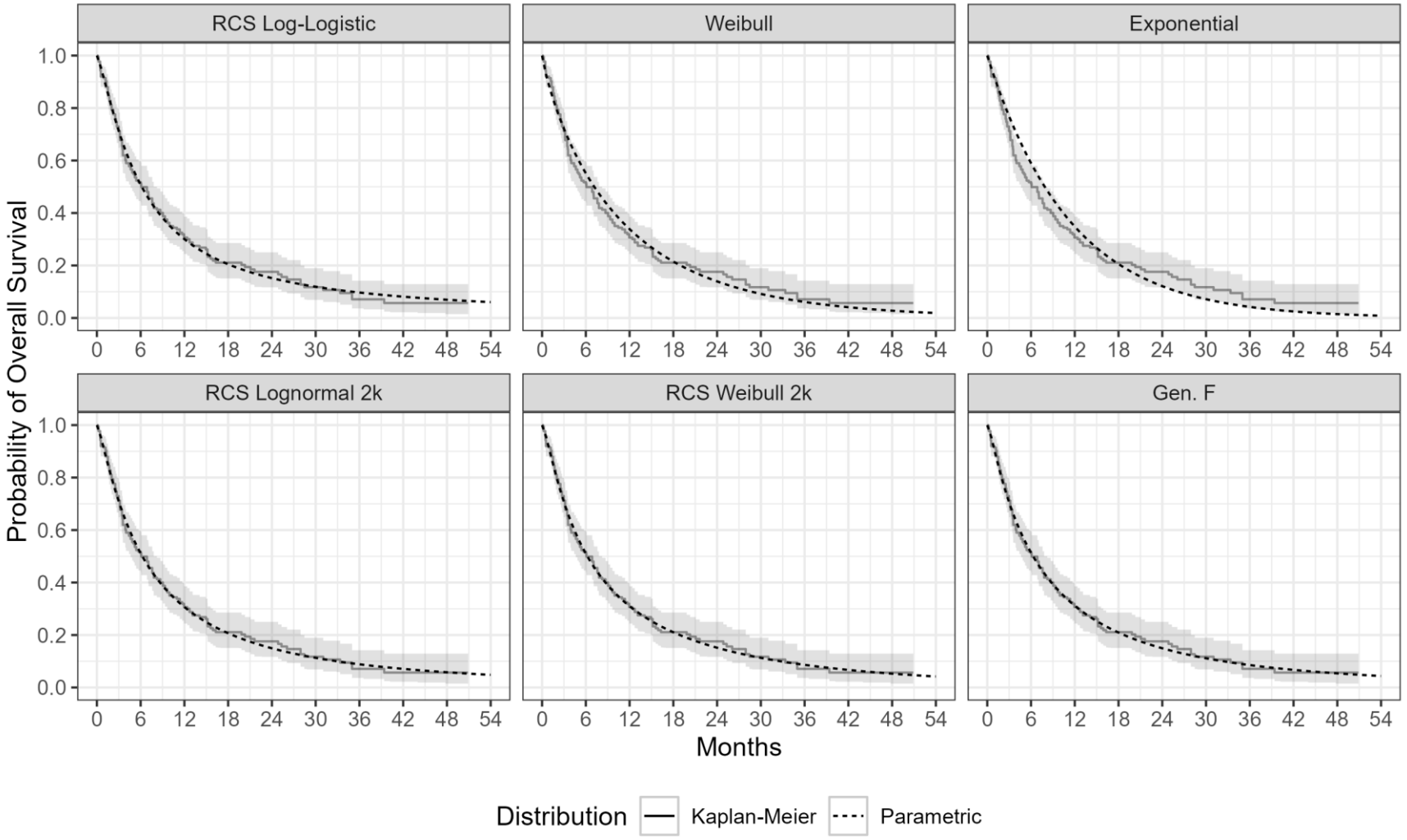


Figure 19. Overall Survival to End of Trial Follow-Up, Pd OS




RCS Log-Logistic
Weibull
Exponential
RCS Lognormal 2k
RCS Weibull 2k
Gen. F
Probability of Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
6
12
18
24
30
36
42
48
54
Months
Distribution
Kaplan-Meier
Parametric

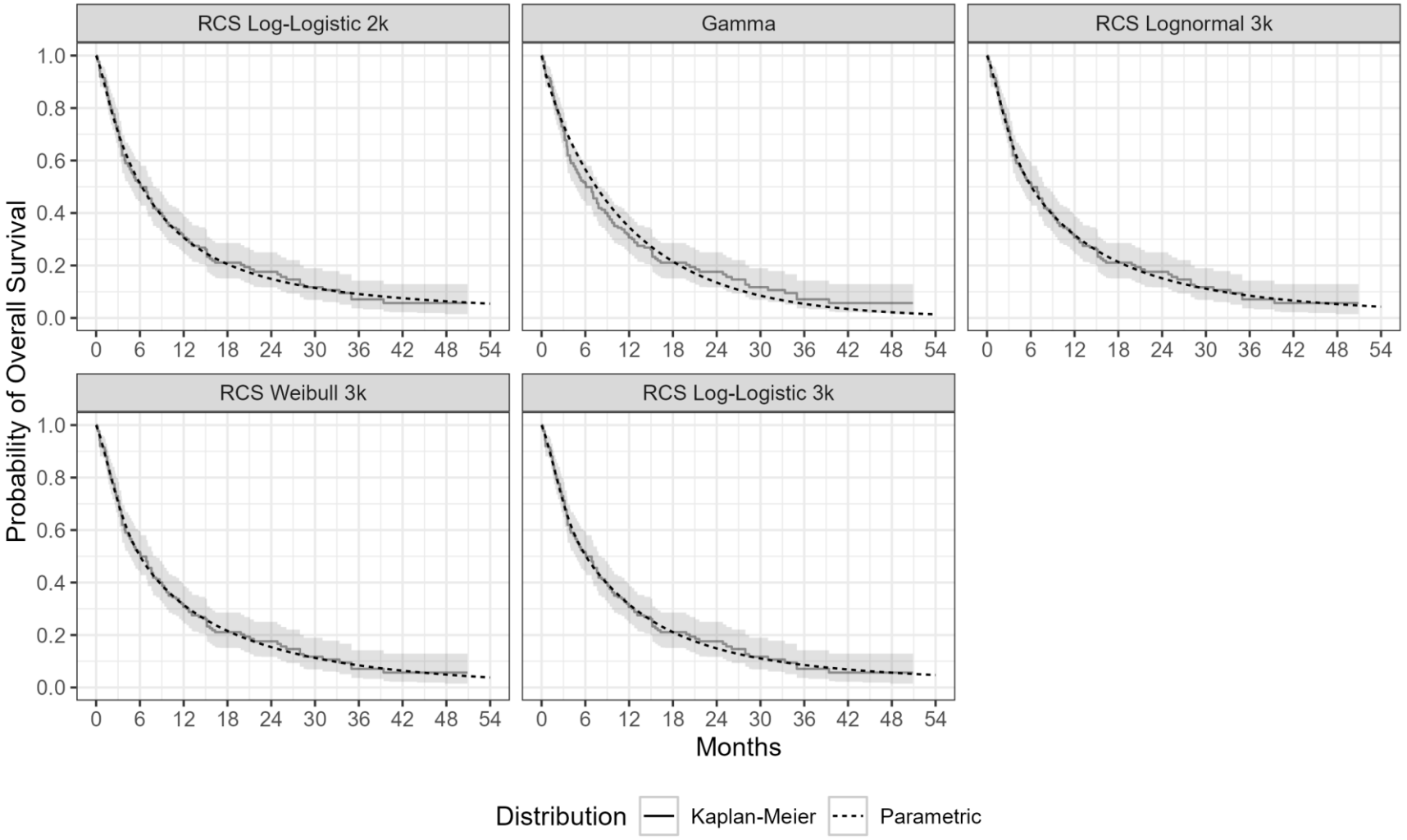
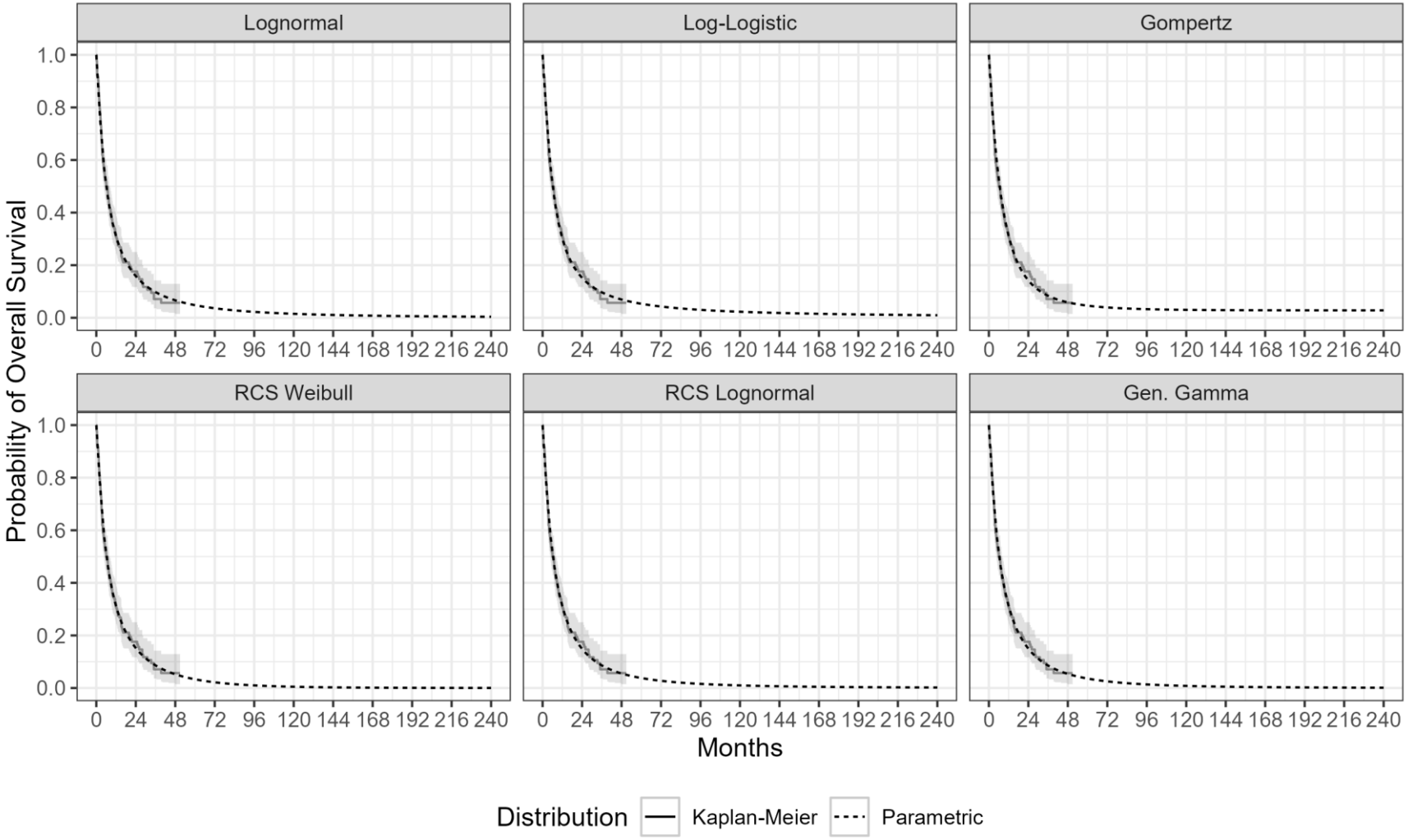
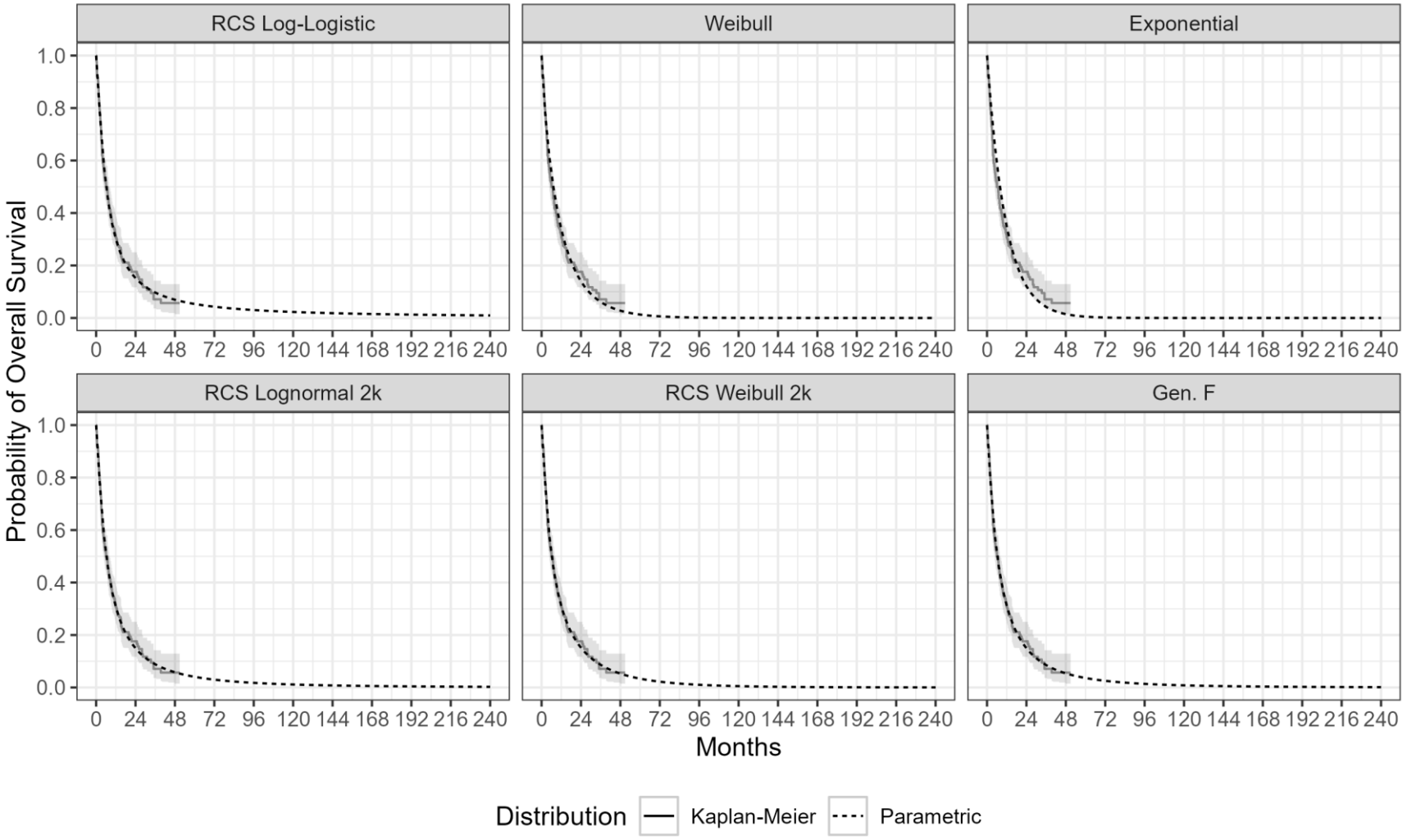
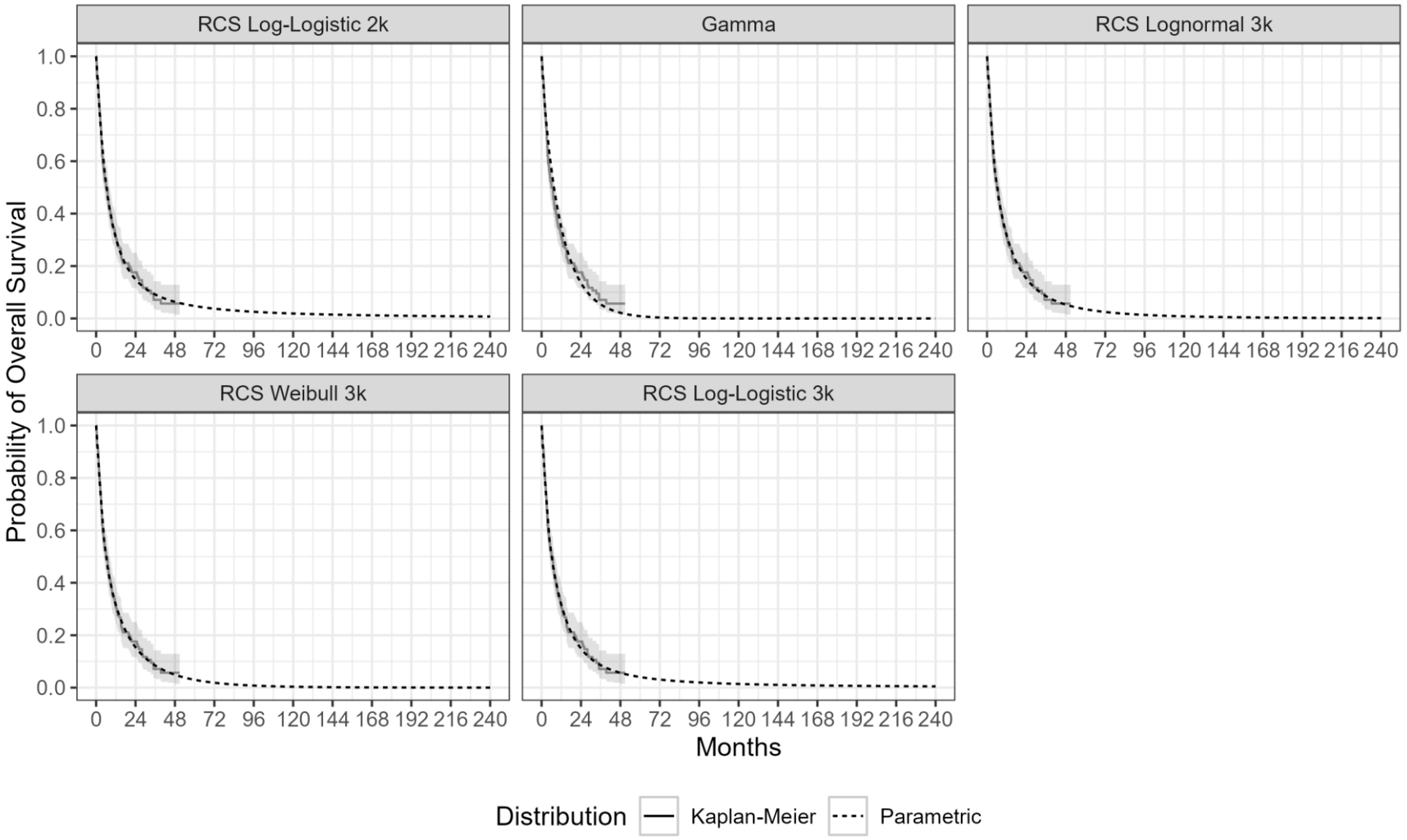

RCS Log-Logistic 2k
Gamma
RCS Lognormal 3k
RCS Weibull 3k
RCS Log-Logistic 3k
Probability of Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
6
12
18
24
30
36
42
48
54
Months
Distribution
Kaplan-Meier
Parametric

Figure 20. Overall Survival to 20 years, Pd OS




RCS Log-Logistic
Weibull
Exponential
RCS Lognormal 2k
RCS Weibull 2k
Gen. F
Probability of Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
0 24 48 72 96 120 144 168 192 216 240
Months
Distribution
Kaplan-Meier
Parametric


RCS Log-Logistic 2k
Gamma
RCS Lognormal 3k
RCS Weibull 3k
RCS Log-Logistic 3k
Probability of Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
0 24 48 72 96 120 144 168 192 216 240
Months
Distribution
Kaplan-Meier
Parametric

Appendix E. Confidential ICER estimates

This appendix reports the results of the cost-effectiveness analysis of IsaPd versus Pd with estimated confidential comparator discounts and [redacted], presented in Table 37.

Table 37: [redacted] for isatuximab and assumed discount on other therapies

Technology	Assumed PAS
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Base case and non-reference case (deterministic) – without modifier

Reference case and non-reference base case (deterministic) results with confidential price estimates are presented in Table 38 to Table 40.

Table 38: Base case results vs Pd SACT (deterministic)- [redacted] for isatuximab and assumed discounts for other therapies

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB†	NMB†
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†WTP threshold of £50,000 assumed. Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab with pomalidomide and dexamethasone; LYG, life years gained; NHB, net health benefit; NMB, net monetary benefit; Pd, pomalidomide and dexamethasone; PAS, patient access scheme; QALYs, quality-adjusted life years; SACT, systemic anti-cancer therapy; WTP, willingness to pay

Table 39: Base case results vs Pd SACT – [redacted] for isatuximab, generic pomalidomide available‡ and assumed discounts for other therapies

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB†	NMB†
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†WTP threshold of £50,000 assumed. ‡ Discount of [redacted] assumed
Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab with pomalidomide and dexamethasone; LYG, life years gained; NHB, net health benefit; NMB, net monetary benefit; Pd, pomalidomide and dexamethasone; PAS, patient access scheme; QALYs, quality-adjusted life years; SACT, systemic anti-cancer therapy; WTP, willingness to pay

Table 40: Base case results vs Pd SACT– [redacted] for isatuximab, pomalidomide backbone cost removed and assumed discounts for other therapies

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB†	NMB†
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†WTP threshold of £50,000 assumed. Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab with pomalidomide and dexamethasone; LYG, life years gained; NHB, net health benefit; NMB, net monetary benefit; Pd, pomalidomide and dexamethasone; PAS, patient access scheme; QALYs, quality-adjusted life years; SACT, systemic anti-cancer therapy; WTP, willingness to pay.

Base case and non-reference case (deterministic) – with modifier

Base case and non-reference case analysis for IsaPd vs Pd SACT applying a 1.2 severity modifier and additionally considering confidential discounts are presented in Table 41 to Table 43.

Table 41. Base-case results vs Pd SACT – [redacted] with 1.2 severity modifier applied

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB†	NMB†
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†WTP threshold of £50,000 assumed. Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + Pd; LYG, life years gained; Pd, pomalidomide + dexamethasone; QALYs, quality adjusted life years; SACT, systemic anti-cancer therapy; vs, versus.

Table 42: Base case results vs Pd SACT – [redacted] for isatuximab, generic pomalidomide available‡ and assumed discounts for other therapies + 1.2 severity modifier applied

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB†	NMB†
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†WTP threshold of £50,000 assumed. ‡ Discount of [redacted] assumed
Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab with pomalidomide and dexamethasone; LYG, life years gained; NHB, net health benefit; NMB, net monetary benefit; Pd, pomalidomide and dexamethasone; PAS, patient access scheme; QALYs, quality-adjusted life years; SACT, systemic anti-cancer therapy; WTP, willingness to pay

Table 43: Base case results vs Pd SACT– [redacted] for isatuximab, pomalidomide backbone cost removed and assumed discounts for other therapies + 1.2 severity modifier applied

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB†	NMB†
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†WTP threshold of £50,000 assumed. Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab with pomalidomide and dexamethasone; LYG, life years gained; NHB, net health benefit; NMB, net monetary benefit; Pd, pomalidomide and dexamethasone; PAS, patient access scheme; QALYs, quality-adjusted life years; SACT, systemic anti-cancer therapy; WTP, willingness to pay.

Scenario analysis (deterministic)

Table 44: Scenarios analysis (deterministic) testing alternative discount assumptions and application of the 1.2 modifier

Scenario name	ICER (£/QALY)- Assumed PAS for all therapies and [redacted]	ICER (£/QALY)- Assumed PAS for all therapies and [redacted] + 1.2 modifier	ICER (£/QALY)- Assumed PAS for all therapies, [redacted] and generic pomalidomide available‡	ICER (£/QALY)- Assumed PAS for all therapies, [redacted] and generic pomalidomide available + 1.2 modifier
No medication wastage	[redacted]	[redacted]	[redacted]	[redacted]
Other costs from DARA NICE submission	[redacted]	[redacted]	[redacted]	[redacted]
20-year time horizon	[redacted]	[redacted]	[redacted]	[redacted]
1.5% effectiveness discount rate	[redacted]	[redacted]	[redacted]	[redacted]
1.5% cost discount rate	[redacted]	[redacted]	[redacted]	[redacted]
1.5% effectiveness and cost discount rates	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L utilities	[redacted]	[redacted]	[redacted]	[redacted]
Isa dosing based on ICARIA weight distribution	[redacted]	[redacted]	[redacted]	[redacted]
Pomalidomide and dexamethasone RDI in IsaPd combination based on RWE	[redacted]	[redacted]	[redacted]	[redacted]
IsaPd SACT TTD/PFS/PFS On-Tx: RCS Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Pd SACT TTD/PFS/PFS-On-Tx: Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Pd SACT TTD/PFS/PFS-On-Tx: RCS Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Isa administered as subcutaneous	[redacted]	[redacted]	[redacted]	[redacted]

IsaPd SACT OS: RCS Lognormal 2k, Pd SACT OS: RCS Weibull	[redacted]	[redacted]	[redacted]	[redacted]
IsaPd SACT OS: RCS Lognormal 2k, Pd SACT OS: Weibull	[redacted]	[redacted]	[redacted]	[redacted]
IsaPd SACT OS: Log-Logistic, Pd SACT OS: RCS Weibull	[redacted]	[redacted]	[redacted]	[redacted]
IsaPd SACT OS: Log-Logistic, Pd SACT OS: Weibull	[redacted]	[redacted]	[redacted]	[redacted]

‡ Discount of [redacted] assumed Abbreviations: ICER, incremental cost-effectiveness ratio; Isa, isatuximab; IsaPd, isatuximab with pomalidomide and dexamethasone; LYG, life years gained; NHB, net health benefit; NMB, net monetary benefit; OS, overall survival; PAS, patient access scheme; Pd, pomalidomide and dexamethasone; QALYs, quality-adjusted life years; RCS, restricted curve splines; SACT, systemic anti-cancer therapy; TTD, time to discontinuation.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [Review of TA658] [ID4067]

Clarification questions

24 October 2023

File name	Version	Contains confidential information	Date
ID4067 MM-Isatuximab clarification letter 091024-[redacted].docx	1.0	No	24th October 2023

Section A: Clarification on effectiveness data

Literature review and searches

A1. Figure 3, Appendix D (PRISMA diagram for total publications relevant to the NICE Decision Problem) - please clarify how the five unique trials identified through the SLR (de novo and update) plus the three unique unpublished trials adds up to seven unique studies. Please confirm that the three unpublished studies mentioned in Figure 3 are the ones listed in Table 18 of Appendix D (and if they are not, please clarify which these studies are). Please also clarify which studies are the five studies identified through the SLR (de novo and update).

Of the total studies identified in the de novo and update review the evidence base considered relevant to the decision problem was as follows:

- 5 unique studies reported in 33 publications were identified in the de novo (2019) and update (2022) review that were relevant to the decision problem (Table 1 and Table 2).
- Following the review, 3 additional documents were provided by Sanofi reporting on 3 data sets/analyses: (1) clinical study report (CSR) reporting the 4th line subgroup from ICARIA-MM (unpublished); (2) IsaPd systemic anti-cancer therapy (SACT) report (unpublished; provided to Sanofi by NHS Digital); and, (3) daratumumab monotherapy SACT report (published within the committee papers for TA783). These are highlighted in bold in Table 1 and Table 2 below. These three publications (1-3) are the ones listed in Table 18 of Appendix D.
- Overall, the evidence base considered relevant to the decision problem comprised 7 unique trials/studies (ICARIA-MM + SIRIUS + COLUMBA + NCT02477891 + REBUILD + IsaPd SACT + Dara SACT) reported in 36 publications were considered relevant to the decision problem (Table 1 and Table 2).
    - Although the 33 publications identified in the review reported on 5 trials and the 3 additional documents reported on 3 trials, the ICARIA-MM trial was identified in both therefore overall, there were 7 unique trials/studies considered relevant to the decision problem. A version of the PRISMA flow diagram has been added below to further clarify (Figure 1).

Table 1. Identified clinical effectiveness evidence: IsaPd

Study name, trial number, phase	Interventions compared	Review	Author, year/source
ICARIA-MM (NCT02990338)	IsaPd vs Pd	De novo SLR (October 2018, updated in June 2019)	Sanofi (protocol) (4);† Sanofi (CSR) (5);† Richardson 2017a (6); Richardson 2017b (7); Richardson 2018 (8)
		Update SLR (October 2022)	Attal 2019 (9); Beksac 2022 (10); Bringhen 2021 (11); Capra 2020 (12); Dimopoulos 2021 (13); Harrison 2021 (14); Houghton 2019 (15); Hulin 2019

			(16); Richardson 2022 (17); Schjesvold 2021 (18); Sunami 2022 (19); **Sanofi 4th line analysis (3)†.**
IsaPd SACT	IsaPd	Update SLR (October 2022)	**SACT (IsaPd) data report (1)†**

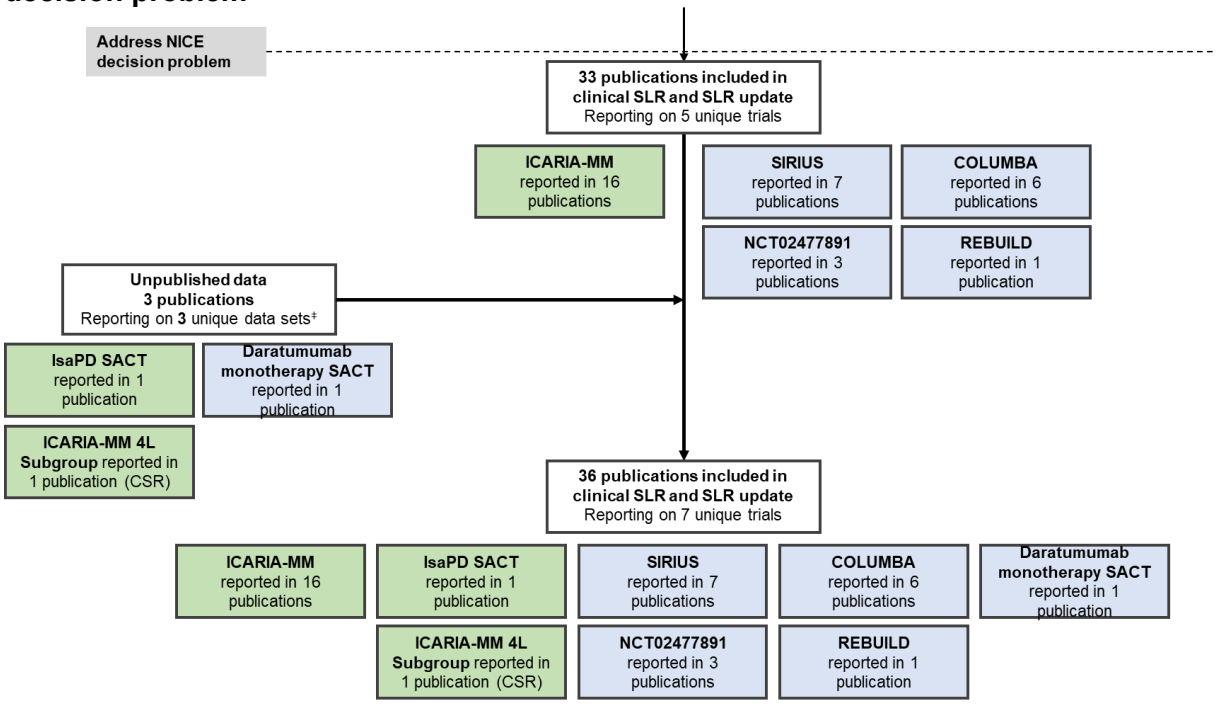
Abbreviations: CADTH, Canadian Agency for Drugs and Therapeutics in Health; Dara, daratumumab; EMA, European Medicines Agency; FDA, Food and Drug Administration; IV, intravenous; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial; SACT, systemic anti-cancer therapy; SC, subcutaneous; SLR, systematic literature review
Notes:
† Unpublished data provided by Sanofi
Studies highlighted in **bold** indicate the studies listed in Appendix D, Section D.2.3.1.3 "Additional information relevant to the NICE decision problem"

Table 2. Identified clinical effectiveness evidence: Daratumumab monotherapy

Study name, trial number, phase	Interventions compared	Review	Author, year/source
SIRIUS	Dara IV	De novo SLR (October 2018, updated in June 2019)	Lonial 2016 (20); CADTH 2016 (21); EMA 2016 (22); FDA 2015 (23); Janssen Research & Development 2013 (24); Lonial 2015 (25); NICE TA510 2017 (26)
		Update SLR (October 2022)	–
COLUMBA	Dara SC vs DARA IV	De novo SLR (October 2018, updated in June 2019)	Mateos 2019 (27); Janssen Research & Development 2017 (28)
		Update SLR (October 2022)	Mateos 2020 (29); Iida 2021 (30); Usmani 2021 (31); Usmani 2022 (32)
NCT02477891	DARA IV	Update SLR (October 2022)	Cook 2021 (33); Alegre 2020 (34); Crusoe 2021 (35)
REBUILD	DARA IV	Update SLR (October 2022)	Terpos 2022 (36)
Dara SACT	Dara	SACT data from data collection period (citation included in Appendix D, Section D.2.3.1.2)	**SACT (Dara) data report (2)**

Abbreviations: CADTH, Canadian Agency for Drugs and Therapeutics in Health; Dara, daratumumab; EMA, European Medicines Agency; FDA, Food and Drug Administration; IV, intravenous; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial; SC, subcutaneous; SLR, systematic literature review
Notes:
Studies highlighted in **bold** indicate the studies listed in Appendix D, Section D.2.3.1.3 "Additional information relevant to the NICE decision problem"

Figure 1. PRISMA flow diagram update to outline identified evidence relevant to the decision problem



Abbreviations: CSR, clinical study report; IsaPd, isatuximab with pomalidomide and dexamethasone; mono, monotherapy; SACT, Systemic Anti-Cancer Therapy; SLR, systematic literature review

A2. Table 20, Appendix D. Please clarify whether or not the references of included studies for the Abodunrin *et al* literature review and meta-analysis (excluded based on study design) were checked for potentially relevant studies relating to daratumumab monotherapy in RRMM, and if not, please clarify the reason. Also, please clarify whether the full texts listed in Table 20 as being 'to hand search' have been hand-searched and if so, what the outcome was

The studies included in the literature review and meta-analysis conducted by Abodunrin (2021 [abstract] (37)) were checked for relevance. The reason for exclusion should more accurately read "SLR/NMA: checked for included studies" as for other reviews.

The Abodunrin (2021) literature review (37) included three studies: CANDOR (2017), CASTOR (2014), and POLLUX (2014).

The citations referred to in the Abodunrin review for CASTOR and POLLUX were both identified in the de novo (2019) literature review as listed in Table 3.

For the 2022 update review, the list of interventions was narrowed to align with the NICE scope more closely and as such daratumumab combination treatments and carfilzomib were no longer in PICO (refer to Appendix D, Section D.1.5.1 for the PICO criteria for the de novo SLR and to Appendix D, Section D.1.5.2 for the PICO criteria for the update SLR). The citation for the CANDOR study was picked up in the update (2022) literature searches but the study was excluded at title/abstract stage as the intervention was not in PICO for the update SLR.

Citations listed with reason for exclusion “SLR To hand search” were checked for references within the date range for the update review. The reason for exclusion should state “SLR/NMA: checked for included studies”.

Table 3: Studies included in the Abodunrin (2021) review vs IsaPd SLRs

Study name, trial number, phase	Interventions compared	Review	Author, year/source
CASTOR	DVd vs Vd	De novo review	**R**efer to Appendix D, Section D.2.3.1.1, Table 16 (**Spencer 2017**; Palumbo 2016; NICE TA573; Jansen Research & Development)
		Update review	Intervention not in PICO for update review (2022)-refer to Appendix D, Section D.1.5.2
POLLUX	DRd vs Rd	De novo review	Refer to Appendix D, Section D.2.3.1.1, Table 16 (**Dimopoulos 2016**; Jansen Research & Development 2014; Moreau 2017; Dimopoulos 2018)
		Update review	Intervention not in PICO for update review (2022)-refer to Appendix D, Section D.1.5.2
CANDOR	KDd vs Kd	De novo review	NA
		Update review	Intervention not in PICO for update review (2022)-refer to Appendix D, Section D.1.5.2 (citation identified by searches but was excluded at title/abstract stage)

Abbreviations: KDd, carfilzomib + daratumumab + dexamethasone; DRd, daratumumab + lenalidomide + dexamethasone; DVd, daratumumab + bortezomib + dexamethasone; IsaPd, isatuximab + pomalidomide + dexamethasone; Kd, carfilzomib + dexamethasone; NA, not applicable; PICO, population, intervention, comparator, outcome; Rd, lenalidomide + dexamethasone; SLR, systematic literature review; Vd, bortezomib + dexamethasone; vs, versus

A3. Appendix D. Identification, selection, and synthesis of clinical evidence, Table 1 (page 17) shows that the electronic database searches were updated until November 2022. In addition, Table 2 (page 18) shows that hand searching was updated until December 2022. Can the company update their searches and confirm that no new and relevant studies have been published since this date?

The Company has updated the clinical-effectiveness evidence searches reported in the company submission (CS) Appendix D. Given the timeframe, the Company has taken a pragmatic approach (i.e., not a full update) to updating these searches as reported below.

Study identification

- Electronic database searches: searches of electronic databases were updated, date limited 13 October 2022 to 20 October 2023 (Table 4).

Table 4. Electronic databases searched

Database / information source	Interface / URL	October 2018†	June 2019†	November 2022‡	October 2023
MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily	Ovid SP	From database inception (1946) to October 2018	From database inception to 27 June 2019	From database inception 12 October 2022 (date limited 28 June 2019 to 12 October 2022)	From 13 October 2022 to the day prior to search
Embase	Ovid SP	From database inception (1974) to October 2018	From database inception to 27 June 2019	From database inception 12 October 2022 (date limited 28 June 2019 to 12 October 2022)	From 13 October 2022 to the day prior to search
Cochrane library – Cochrane Central Register of Controlled Trials	Wiley Cochrane Library / EBM Reviews†	NR	Coverage dates not found; Issue 6 of 12, June 2019	<2005 to October 12, 2022> (date limited to 2019 to Current)	<2005 to October 12, 2022> (date limited to 2023 to Current)
Cochrane library – Cochrane Database of Systematic Reviews	Wiley Cochrane Library / EBM Reviews†	NR	Coverage dates not found; Issue 6 of 12, June 2019	<September 2022> (date limited to 2019 to Current)	<September 2022> (date limited to 2023 to Current)
Cochrane library – Database of Abstracts of Reviews of Effects†	CRD	Coverage dates not found‡	Coverage dates not found‡	Not searched‡	Not searched‡
Cochrane library – Health Technology Assessment†	CRD	Coverage dates not found¶	Coverage dates not found¶	Not searched¶	Not searched¶

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; EED, Economic Evaluation Database; HTA, Health Technology Assessment; ICER, incremental cost effectiveness ratio; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicines Consortium.
Notes:
†Wiley Cochrane Library interface used to search Cochrane CENTRAL and CDSR in the de novo SLR and EBM Reviews used to search Cochrane CENTRAL and CDSR in the update SLR (November 2022); ‡The CRD databases are no longer included in the Cochrane library, from 7th August 2018. CRD are maintaining versions of DARE and NHS EED until at least 2021, with records published on DARE and NHS EED until 31st March 2015. From 31st March 2018, CRD is no longer adding records to the HTA database. More details available at: https://www.crd.york.ac.uk/CRDWeb/ and https://onlinelibrary.wiley.com/doi/abs/10.1002/jrsm.1235.

Grey literature searches: searches of health technology assessment agency (HTA) websites and the clinical trial registries were updated, date limited December 2022 to Current (Table 5).

Table 5. Hand searching sources

	October 2018†	June 2019†	December 2022‡	October 2023
Conference proceedings				
ASCO	✓	✓	✓	×
ESMO	✓	✓	✓	×
EHA	✓	✓	✓	×
ASH	✓	✓	✓	×
ESH	✓	✓	✓	×
Clinical trial registries				
World Health Organisation International Clinical Trials Registry Platform	✓	✓	✓	✓
US National Institute for Health (NIH) clinical trials.gov	×	×	✓	✓
HTA body websites				
England and Wales: NICE	✓	✓	✓	✓
Scotland: SMC	✓	✓	✓	✓
Canada: CADTH	✓	✓	✓	✓
USA: ICER	✓	✓	✓	✓
Australia: PBAC	×	×	✓	✓
France: HAS	×	×	✓	✓
Other grey literature sources				
Drugs@FDA	✓	✓	✓	×
EMA	×	×	✓	×
EQ-5D	×	×	✓	×
Reference lists	✓	✓	✓	✓
Clinical study reports	×	×	✓	×

†Referred to as de novo SLR; ‡Referred to as SLR update.
Abbreviations: American Society of Clinical Oncology; ASH, American Society of Hematology; CADTH, Canadian Agency for Drugs and Technologies in Health; EHA, European Hematology Association; EMA, European Medicines Agency; EQ-5D, EuroQol five-dimension; ESH, European Society of Hematology; ESMO, European Society for Medical Oncology; FDA, Food and Drug Administration; ICER, Institute for Clinical and Economic Review; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; SMC Scottish Medicines Consortium; US, United States.

Study selection

A single reviewer removed obviously irrelevant records, such as animal studies, commentaries and news items, and records on issues unrelated to the topic of interest. One reviewer independently screened the remaining records' title and abstracts within the Covidence package (38). Ineligible records were excluded. Following the retrieval of full text documents, one reviewer independently screened the full text documents within Covidence to make the final selection of eligible studies. Ineligible studies were excluded and the reason for exclusion was recorded. Included studies were confirmed by a second reviewer.

Excluded studies at title/abstract and full-text screening stage were spot checked by a second reviewer. Any disagreements about inclusion were resolved through discussion.

Hand searches were conducted by a single reviewer.

Eligibility criteria were as reported in CS Appendix D (refer to Section D.1.5.2, Table 4).

Results

New clinical evidence relevant to the decision problem are not expected to be identified, but an updated report summarising any newly identified clinical effectiveness evidence will be provided in due course for completeness.

A4. Appendix G. Published cost-effectiveness studies, Table 22 (page 234), the electronic database searches were updated until November 2022. In addition, Table 23 (page 235) shows that hand searching was updated until December 2022. Can the company update their searches and confirm that no new and relevant studies have been published since this date?

The company has updated the cost-effectiveness evidence searches reported in Appendix G. Given the timeframe, Sanofi has taken a pragmatic approach (i.e., not a full update) to updating these searches as reported below.

Study identification

- Electronic database searches: searches of electronic databases were updated, date limited 8 November 2022 to 13 October 2023 (Table 6).

- Grey literature searches: searches of health technology assessment agency (HTA) websites and the Cost Effectiveness Analysis Registry were updated, date limited December 2022 to 13 October 2023 (Table 7).

Table 6. Electronic databases searched

Database / information source	Interface / URL	October 2018†	June 2019†	November 2022‡	*October 2023*
MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily	Ovid SP	From database inception to October 2018	From database inception to 27 June 2019	From 28 June 2019 to the day prior to search	From 8 November 2022 to the day prior to search
Embase	Ovid SP	From database inception to October 2018	From database inception to 27 June 2019	From 28 June 2019 to the day prior to search	From 8 November 2022 to the day prior to search
NHS Economic Evaluation Database (NHS EED)	Centre for Reviews and Dissemination website	From database inception to October 2018	From database inception to 28 June 2019¶	Not searched¶	Not searched¶
Health Technology Assessment (HTA) database	Centre for Reviews and Dissemination website	From database inception to October 2018	From database inception to 28 June 2019¶	Not searched¶	Not searched¶

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; EED, Economic Evaluation Database; HTA, Health Technology Assessment; ICER, incremental cost effectiveness ratio; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicines Consortium.
Notes:†Referred to as Original Review (#1); ‡Referred to as Update Review (#2); ¶The CRD databases are no longer included in the Cochrane library, from 7th August 2018. CRD are maintaining versions of DARE and NHS EED until at least 2021, with records published on DARE and NHS EED until 31st March 2015. From 31st March 2018, CRD is no longer adding records to the HTA database. More details available at: https://www.crd.york.ac.uk/CRDWeb/ and https://onlinelibrary.wiley.com/doi/abs/10.1002/jrsm.1235

Table 7. Hand searching sources

	October 2018†	June 2019†	December 2022‡	October 2023
Conference proceedings				
ASCO	✓	✓	✓	×
ESMO	✓	✓	✓	×
EHA	✓	✓	✓	×
ASH	✓	✓	✓	×
ESH	✓	✓	✓	×
HTA body websites				
England and Wales: NICE	✓	✓	✓	✓
Scotland: SMC	✓	✓	✓	✓
Canada: CADTH	✓	✓	✓	✓
USA: ICER	✓	✓	✓	✓
Australia: PBAC	×	×	✓	✓
France: HAS	×	×	✓	✓

	October 2018†	June 2019†	December 2022‡	October 2023
Economic websites				
Cost Effectiveness Analysis Registry	✓	✓	✓	✓
EconPapers within RePEc)	×	×	✓	×
EQ-5D	×	×	✓	×
University of Sheffield ScHARRHUD database	✓	✓	✓	×
HTA Database of the INAHTA	×	×	✓	×
Reference lists	✓	✓	✓	✓

Abbreviations: American Society of Clinical Oncology; ASH, American Society of Hematology; CADTH, Canadian Agency for Drugs and Technologies in Health; EHA, European Hematology Association; ESH, European Society of Hematology; ESMO, European Society for Medical Oncology; EQ-5D, EuroQol five-dimension; HAS, Haute Autorité de Santé; HTA, Health Technology Assessment; ICER, Institute for Clinical and Economic Review; INAHTA, International Network of Agencies for Health Technology Assessment; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; RePEc, Research Papers in Economics; SMC Scottish Medicines Consortium
Notes: †Referred to as Original Review (#1); ‡Referred to as Update Review (#2)

Study selection

A single reviewer removed obviously irrelevant records, such as animal studies, commentaries and news items, and records on issues unrelated to the topic of interest. One reviewer independently screened the remaining records' title and abstracts within the Covidence package (38). Ineligible records were excluded. Following the retrieval of full text documents one reviewer independently screened the full text documents within Covidence to make the final selection of eligible studies. Ineligible studies were excluded and the reason for exclusion was recorded. Included studies were confirmed by a second reviewer. Excluded studies at title/abstract and full-text screening stage were spot checked by a second reviewer. Any disagreements about inclusion were resolved through discussion.

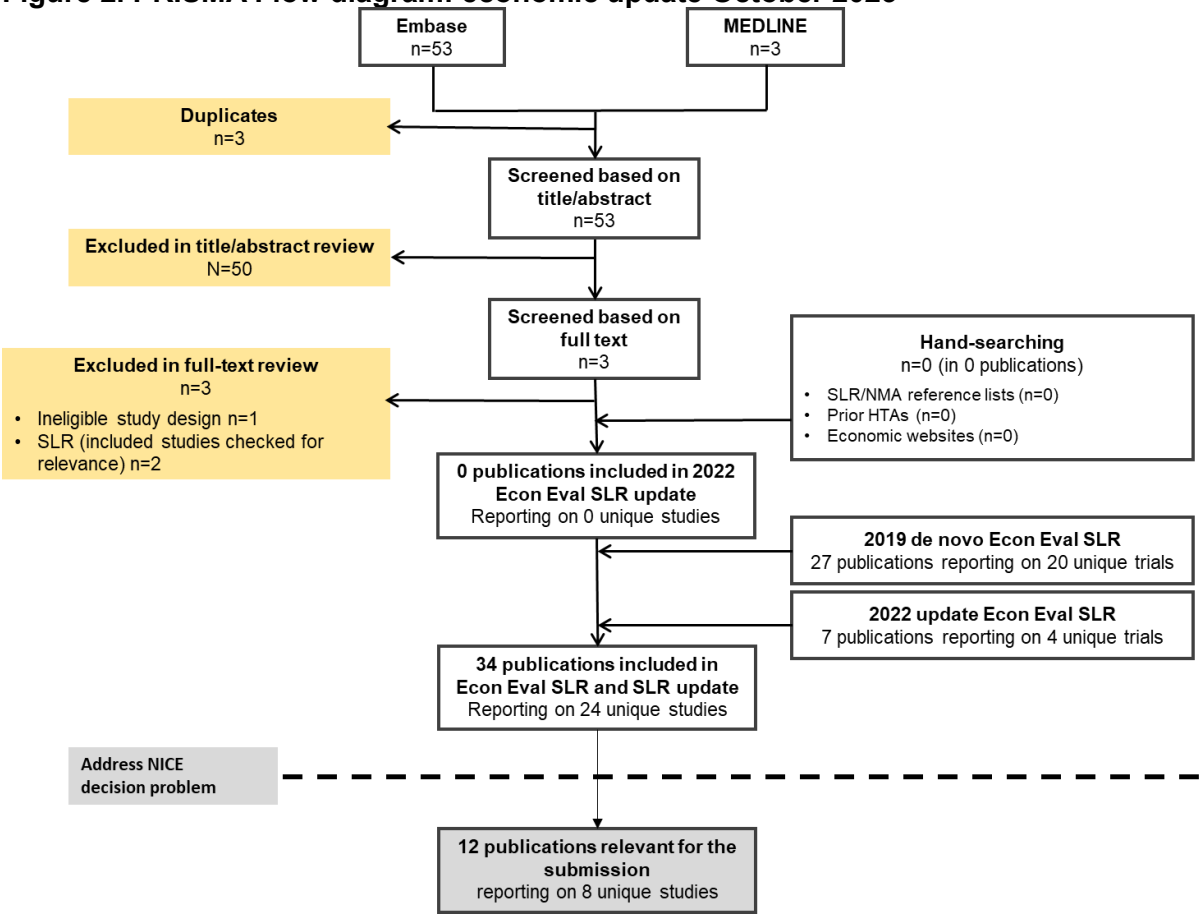
Hand searches were conducted by a single reviewer.

Eligibility criteria were as reported in CS Appendix G (refer to Section G.1.3, Table 30).

Results

The searches conducted in October 2023 retrieved 56 records. No records were identified in supplementary searches. Following deduplication, 53 records were assessed for relevance; of these 50 records were excluded after assessment of information in the title and abstract. Three publications were assessed at full text; all were excluded. A list of studies excluded at full text with reason for exclusion is provided in Table 8. The study selection process is provided in Figure 2.

Figure 2. PRISMA Flow diagram: economic update October 2023



Abbreviations: HTA, health technology assessment; NMA, network meta-analysis; SLR, systematic literature review.

Table 8. List of excluded studies at full-text with reason for exclusion

Citation	Reason for exclusion
Almajed S, Alotaibi N, Zulfiqar S, Dhuhaibawi Z, O'Rourke N, Gaule R, et al. Cost-effectiveness evidence on approved cancer drugs in Ireland: the limits of data availability and implications for public accountability. European Journal of Health Economics. 2022;23(3):375-431.	Review of prior National Center for Pharmacoeconomic (NCPE; Ireland) review of approved cancer drugs. 1 HTA report (daratumumab) (2018) was identified, outside of the date parameters for the update)
Asra A, Pillidge Z, Clark A, Ronchi M, Zayas J, Fernandez Munoz A, et al. HSD42 Modelling Time and Costs Associated With Daratumumab Treatment Delivery in the Home Care Setting Versus the Hospital in Spain to Understand Potential Benefits to Patients and Hospitals. Value in Health. 2022;25(12 Supplement):S281.	Study design: not a cost-effectiveness, cost-utility, cost-minimisation study
Choon-Quinones M, Zelei T, Nemeth B, Toth M, Jia XY, Barnett M, et al. Systematic literature review of health economic models developed for multiple myeloma to support future analyses. Journal of Medical Economics. 2023;26(1):110-9.	Systematic review: included studies checked for relevance (NICE TA658 IsaPd and Lo Muto 2017 daratumumab monotherapy, already captured in previous searches)

Abbreviations: HTA, health technology assessment; NCPE, National Centre for Pharmacoeconomics; NICE, National Institute for Healthcare and Excellence.

Clinical data

A5. It is unusual that median treatment durations and median survival are longer than median follow-up. Please clarify that the data presented (for example, in the box opening B.2 it is reported that median OS was 18.8 months with a median follow up of 9.4 months, and that median treatment duration with IsaPd was 8.9 months with a median follow up of 5.9 months) are correct.

The reported data were taken directly from the IsaPd CDF SACT report (1) as provided by NHS Digital, provided in the reference pack. The definitions and data from the report are summarised below.

The data linked to the query have been reproduced from the SACT report (1) with cross references to the source file below.

CDF and EAMS combined cohort

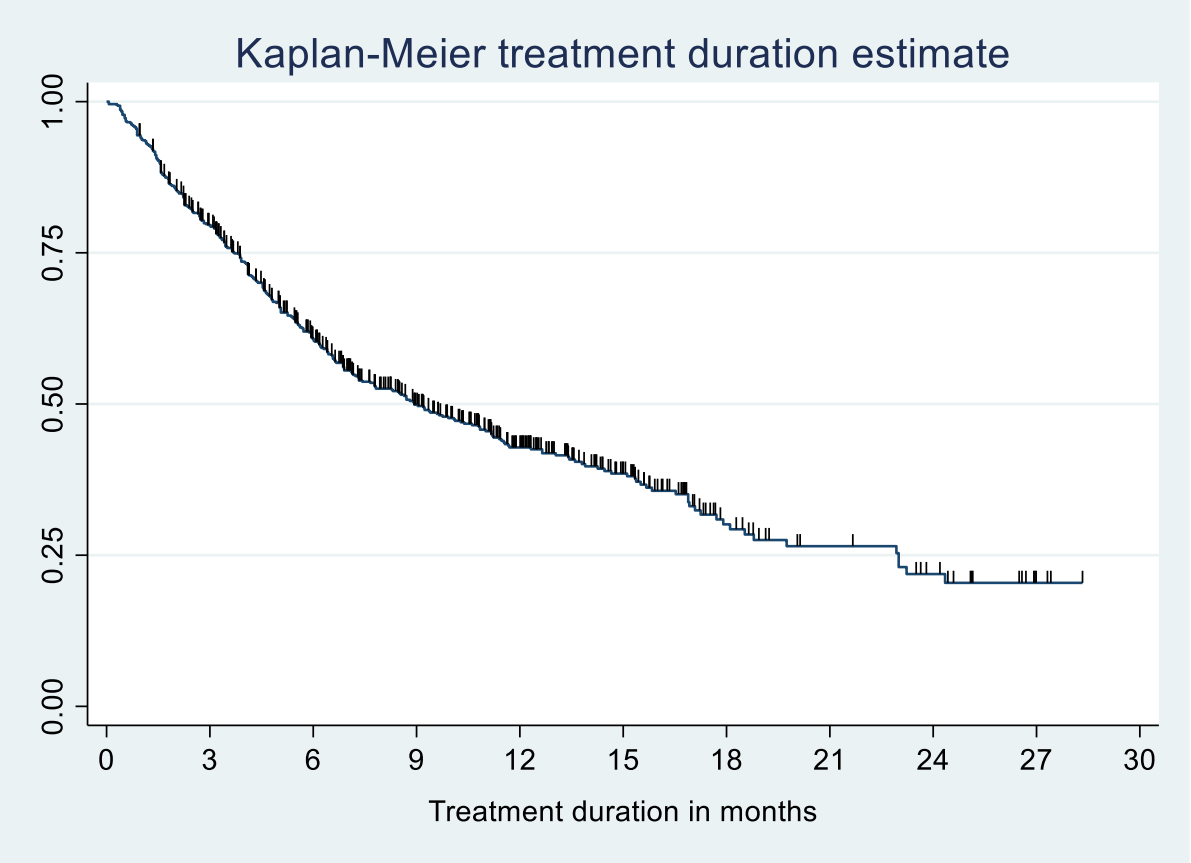
The SACT report states that the median follow-up time in the CDF and EAMS combined cohort was 5.9 months. The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT plus prescription length (1). Presently, 94% (N=132) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of 18.5 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides a maximum follow-up period of 19.5 months. SACT follow-up ends 30 April 2022 (1).

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT (1).

The Kaplan-Meier curve for ongoing treatment is shown in Figure 3. The median treatment duration for all patients was 8.9 months [95% CI: 7.3, 10.8] (270 days) (N=736) (1).

Figure 3. Kaplan-Meier treatment duration (N=736)



Source: Figure 4 of IsaPd CDF SACT report (1)
Note: One patient died on the same day they started treatment, and as such, they were excluded from the model as their treatment duration was zero days.

Table 9 and Table 10 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 29 months (882 days). SACT contains more follow-up for some patients (1).

Table 9. Number of patients at risk, by quarterly breakpoints (CDF and EAMS combined cohort)

Time intervals (months)	0-27	3-27	6-27	9-27	12-27	15-27	18-27	21-27	24-27	27
Number at risk	736	552	357	237	146	88	37	24	16	3

Source: Table 26 of IsaPd CDF SACT report (1)

Table 10 shows that for all patients who received treatment, 20 were still on treatment (censored) at the date of follow-up and 55 had ended treatment (events) (1).

Table 10. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored) (CDF and EAMS combined cohort)

Time intervals (months)	0-27	3-27	6-27	9-21	12-27	15-27	18-27	21-27	24-27	27
Censored	344	308	234	173	111	65	28	19	15	3
Events	392	244	123	64	35	23	9	5	1	0

Source: Table 27 of IsaPd CDF SACT report (1)

Overall survival (OS)

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring) (1).

Of the 737 patients with a treatment record in SACT, the minimum follow-up was 4.8 months (146 days) from the last CDF application. Patients were traced for their vital status on 24 August 2022. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time was 9.4 months (286 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date. The median OS was 18.8 months [95% CI: 15.7, 22.9] (572 days) (1).

Table 11 and Table 12 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 32.7 months (995 days), all patients were traced on 24 August 2022 (1).

Table 11. Number of patients at risk, by quarterly breakpoints (CDF and EAMS combined cohort)

Time intervals (months)	0-30	3-30	6-30	9-30	12-30	15-30	18-30	21-30	24-30	27-30	30
Number at risk	736	628	525	381	283	191	103	45	30	21	4

Source: Table 37 of IsaPd CDF SACT report (1)

Table 12 shows that for all patients who received treatment, 425 were still alive (censored) at the date of follow-up and 311 had died (events) (1).

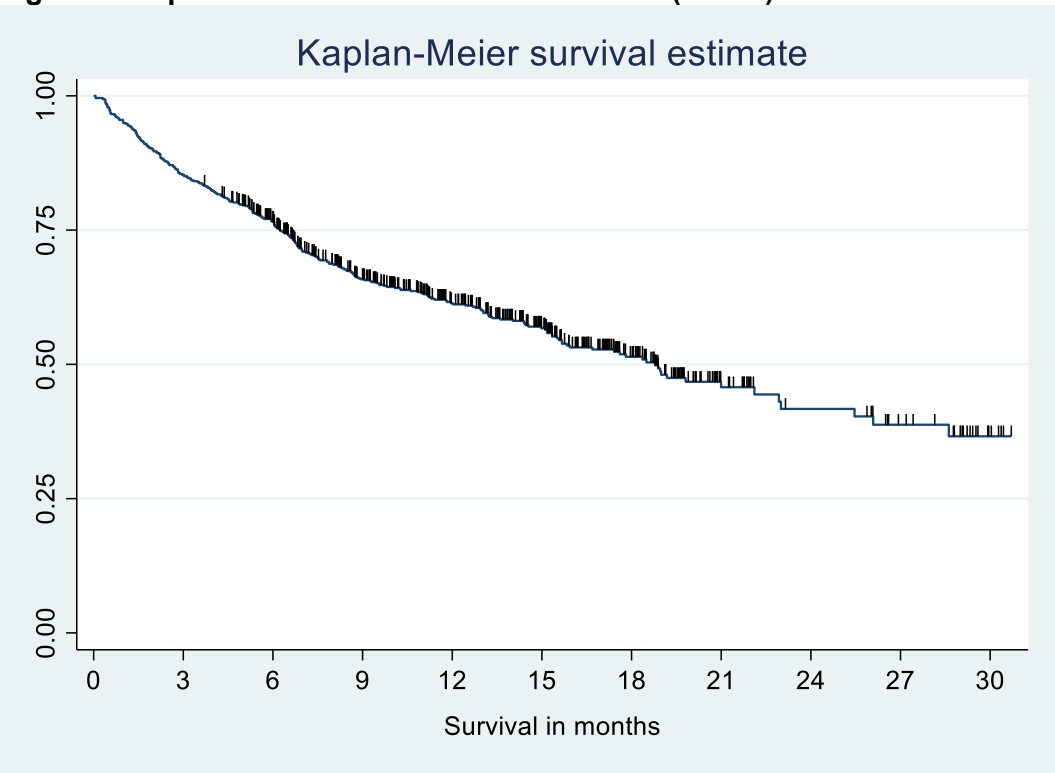
Table 12. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored) (EAMS cohort)

Time intervals (months)	0-30	3-30	6-30	9-30	12-30	15-30	18-30	21-30	24-30	27-30	30
Censored	425	425	385	309	234	161	88	39	27	20	4
Events	311	203	140	72	49	30	15	6	3	1	0

Source: Table 38 of IsaPd CDF SACT report (1)

Figure 4 provides the Kaplan-Meier curve for OS, censored at 24 August 2022. The median OS was 18.8 months [95% CI: 15.7, 22.9] (572 days) (1).

Figure 4. Kaplan-Meier overall survival estimate (n=736)



Note: One patient died on the same day they started treatment, and as such, they were excluded from the model as their treatment duration was zero days
Source: Figure 7 of IsaPd CDF SACT report (1)

A6. Please clarify why in treatment duration for ID4067 is not available (CS Table 7).

This was a reporting error; Sanofi confirm that treatment duration was reported in both TA658 and the current appraisal. In both appraisals, treatment duration for ICARIA-MM was calculated as time to discontinuation (TTD).

A7. In CS Table 17, values for MRD status with greater than or equal to two samples are not reported. Please clarify whether the numbers are zero or data are missing.

MRD status with greater than or equal to two samples data are zero in the post-hoc analysis of the 4th line population of ICARIA-MM (refer to 1.5.10 “Summary of MRD status – ITT population” of the CSR report in the reference pack).

A8. In CS Table 18 the data appear inconsistent, for example, in Cycle 14 the IsaPd group has a value of 0.80 which is stated to be a 0.07 increase from baseline, however in Cycle 15 a value of 0.79 is associated with an increase of 0.02 implying a different baseline value. Is the reason for this because different patients have completed the questionnaire?

The data have been checked vs the post-hoc CSR for the 4th line subgroup (1.8.1.1: “EQ-5D-5L – Health state utility index value – Descriptive statistics by visit – Safety population evaluable for health state utility index”). Different patients completed the questionnaire at

different timepoints. Table 18 from CS has been updated to include the number of participants for the Pd and IsaPd arms at each treatment cycle where data was available (Table 13).

Table 13. ICARIA-MM key secondary endpoint – EQ-5D-5L HSUV, 4th-line (safety population†) [Update to CS Table 18]

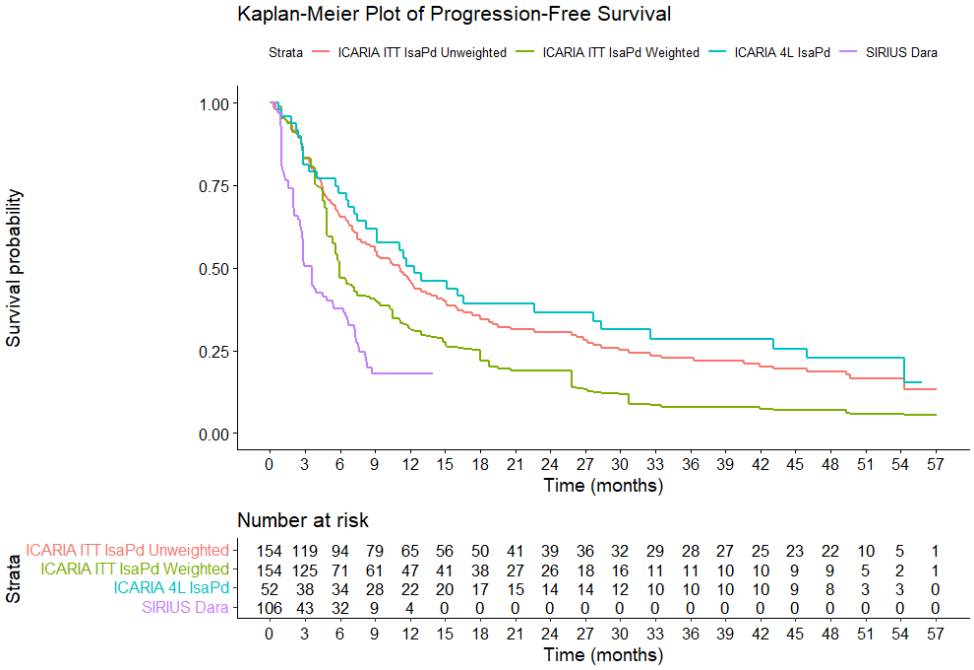
Timepoint	Pd			IsaPd		
	N	Mean (SD)†	CFB	N	Mean (SD)†	CFB
Baseline	53	0.66 (0.25)	–	48	0.74 (0.20)	–
Treatment Cycle 2‡	49	0.71 (0.24)	0.04 (0.24)	44	0.74 (0.25)	0.00 (0.20)
Treatment Cycle 3‡	43	0.73 (0.21)	0.03 (0.19)	45	0.73 (0.25)	–0.00 (0.20)
Treatment Cycle 4‡	40	0.74 (0.25)	0.05 (0.27)	43	0.78 (0.22)	0.04 (0.19)
Treatment Cycle 5‡	34	0.70 (0.20)	0.02 (0.24)	38	0.78 (0.24)	0.05 (0.19)
Treatment Cycle 6‡	27	0.74 (0.25)	0.05 (0.23)	36	0.77 (0.17)	0.01 (0.14)
Treatment Cycle 7‡	28	0.69 (0.25)	0.01 (0.29)	35	0.75 (0.20)	–0.00 (0.16)
Treatment Cycle 8‡	25	0.71 (0.26)	0.00 (0.28)	33	0.74 (0.27)	–0.01 (0.24)
Treatment Cycle 9‡	23	0.68 (0.34)	–0.04 (0.35)	28	0.76 (0.16)	0.01 (0.13)
Treatment Cycle 10‡	21	0.68 (0.26)	–0.03 (0.27)	28	0.81 (0.15)	0.05 (0.17)
Treatment Cycle 11‡	21	0.66 (0.17)	–0.00 (0.30)	26	0.75 (0.17)	0.01 (0.15)
Treatment Cycle 12‡	17	0.72 (0.19)	–0.01 (0.25)	21	0.76 (0.19)	0.01 (0.12)
Treatment Cycle 13‡	16	0.72 (0.22)	–0.00 (0.24)	20	0.77 (0.14)	0.03 (0.13)
Treatment Cycle 14‡	11	0.73 (0.23)	0.06 (0.28)	13	0.80 (0.14)	0.07 (0.14)
Treatment Cycle 15¶	9	0.72 (0.24)	0.11 (0.35)	11	0.79 (0.18)	0.02 (0.10)
EOT§	26	0.58 (0.33)	–0.12 (0.32)	18	0.45 (0.30)	–0.27 (0.19)

†A higher score represents a better level of quality of life; ‡At Day 1.¶ One patient was added at cycle 3 and because more data were collected at cycle 15, this cycle was added to the EQ-5D-5L descriptive analysis; §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 + dexamethasone; MM, multiple myeloma; Pd, pomalidomide + dexamethasone; SD, standard deviation.

A9. Please add the unweighted Kaplan-Meier (KM) curve for the 4th line subgroup of ICARIA-MM in the IsaPd arm to Figure 13 and Figure 14 in Appendix P.

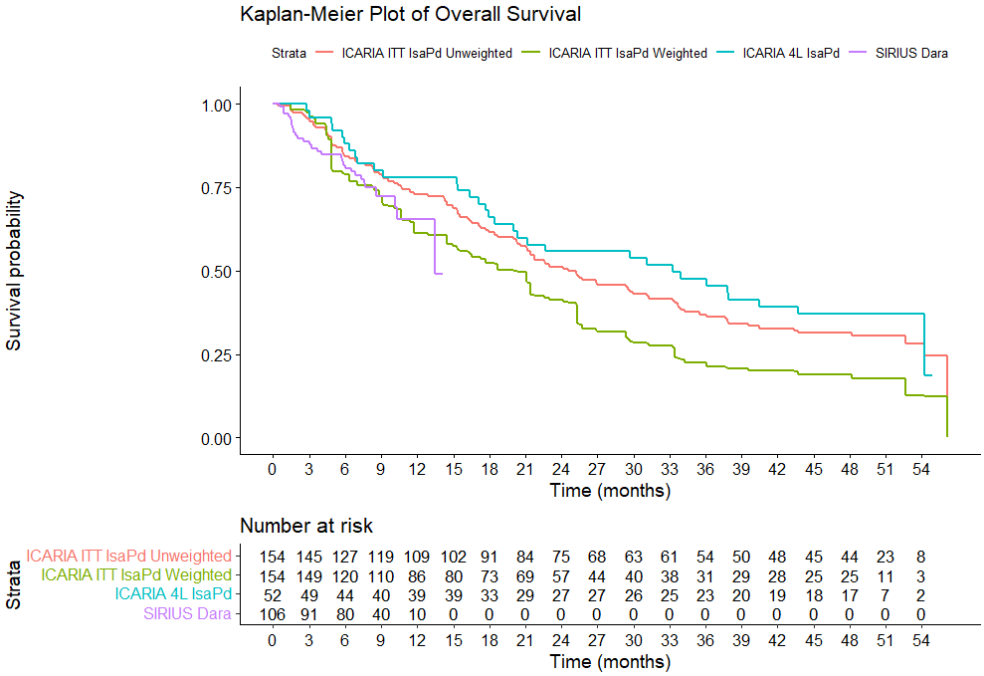
The two updated figures with the addition of the unweighted KM curve for 4th line IsaPd arm for progression free survival (PFS) (Figure 5) and OS (Figure 6) have been provided below.

Figure 5. Kaplan-Meier for PFS for IsaPd in ICARIA-MM vs. daratumumab monotherapy in SIRIUS [Figure 13 in CS: Appendix P]



Abbreviations: 4L, 4th line; CS, company submission; Dara, daratumumab; IsaPd, isatuximab + pomalidomide + dexamethasone; ITT, intention to treat; PFS, progression free survival; vs, versus.

Figure 6. Kaplan-Meier for OS for IsaPd in ICARIA-MM vs. daratumumab monotherapy in SIRIUS (Figure 14 in CS: Appendix P)



Abbreviations: 4L, 4th line; CS, company submission; Dara, daratumumab; IsaPd, isatuximab + pomalidomide + dexamethasone; ITT, intention to treat; OS, overall survival; vs, versus.

A10. CS p78 states that 'Note that compared with what was reported in the SACT reports for daratumumab and IsaPd, the event numbers for OS and treatment duration are not exact in our analyses.' Please provide the original SACT KM plot and the number at risk for OS and treatment duration for the IsaPd arm and daratumumab monotherapy arm.

The daratumumab monotherapy data used in our analyses were taken from the daratumumab SACT report which were reported in the NICE committee papers of TA783 (provided in the reference pack). The Kaplan-Meier curves for treatment duration, overall survival, and numbers at risk from this report are provided below.

The IsaPd data used in our analyses were taken from the IsaPd CDF SACT report (1) as provided by NHS Digital, provided in the reference pack. The Kaplan-Meier curves for treatment duration and overall survival for the CDF and EAMS combined cohort from the SACT report for IsaPd are provided in response to A5.

As noted in the CS, the digitisation process from the available SACT KM curves was not able to obtain an exact match. We believe this is due the large number of patients and events which makes the KM curve very busy and causes difficulty in capturing each point at which the KM curves step down. The "tot.events=" argument was used in the getIPDR code in R to set the total number of events, however an exact match was still not obtained.

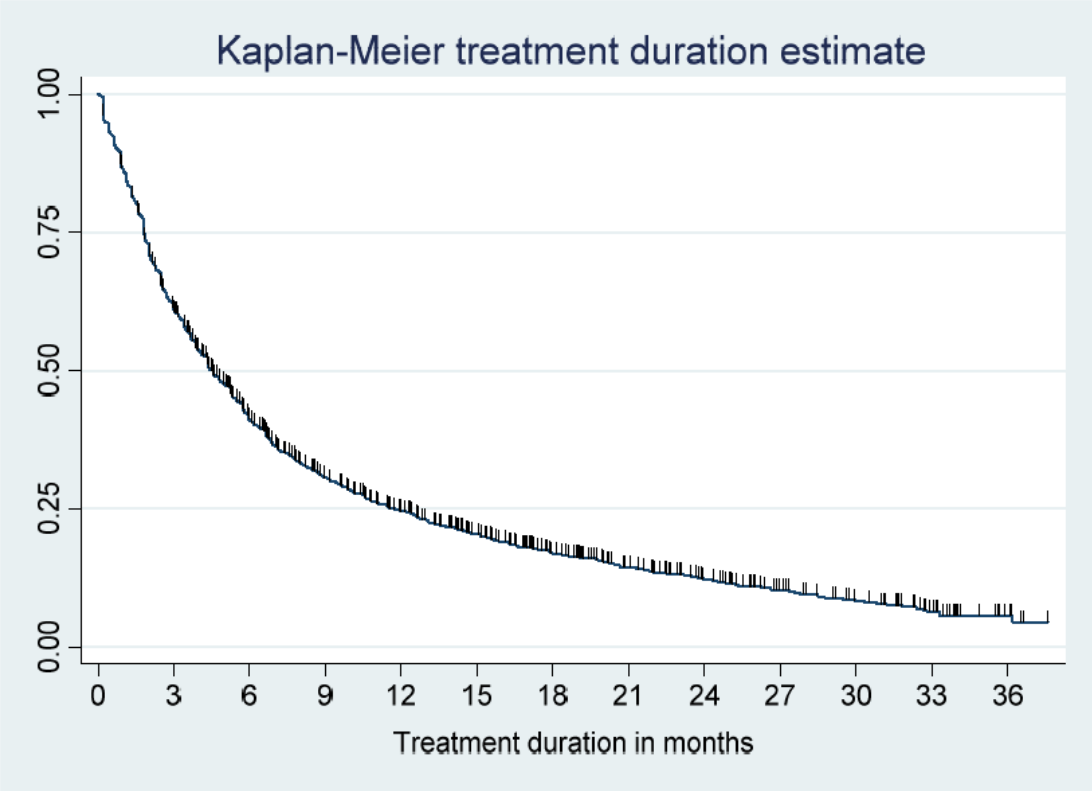
Nevertheless, as noted in the CS, the difference was more pronounced for the Dara SACT curves than for IsaPd SACT curves as there are more patients/events in the former. The number of reported events for treatment duration and OS for IsaPd and daratumumab monotherapy arms and the number of events captured in the reconstructed dataset used in the company economic analysis are presented in Table 14 for reference. The events generated after reconstruction of daratumumab monotherapy outcomes (1,387 events for daratumumab OS in SACT data vs 1,367 in reconstructed SACT data) is most likely to have a positive effect on the daratumumab monotherapy arm due to more patients remaining alive/on treatment with daratumumab monotherapy in the reconstructed data.

Table 14. Reported event counts for IsaPd and Daratumumab monotherapy in SACT reports vs reconstructed dataset

Treatment arm	Overall survival		Treatment duration	
	SACT reported events	Reconstructed events	SACT reported events	Reconstructed events
IsaPd	311	309	392	390
Daratumumab monotherapy	1387	1367	1876	1839

Abbreviations: SACT, IsaPd systemic anti-cancer therapy.

Figure 7. Kaplan-Meier treatment duration (n=2,300): daratumumab monotherapy

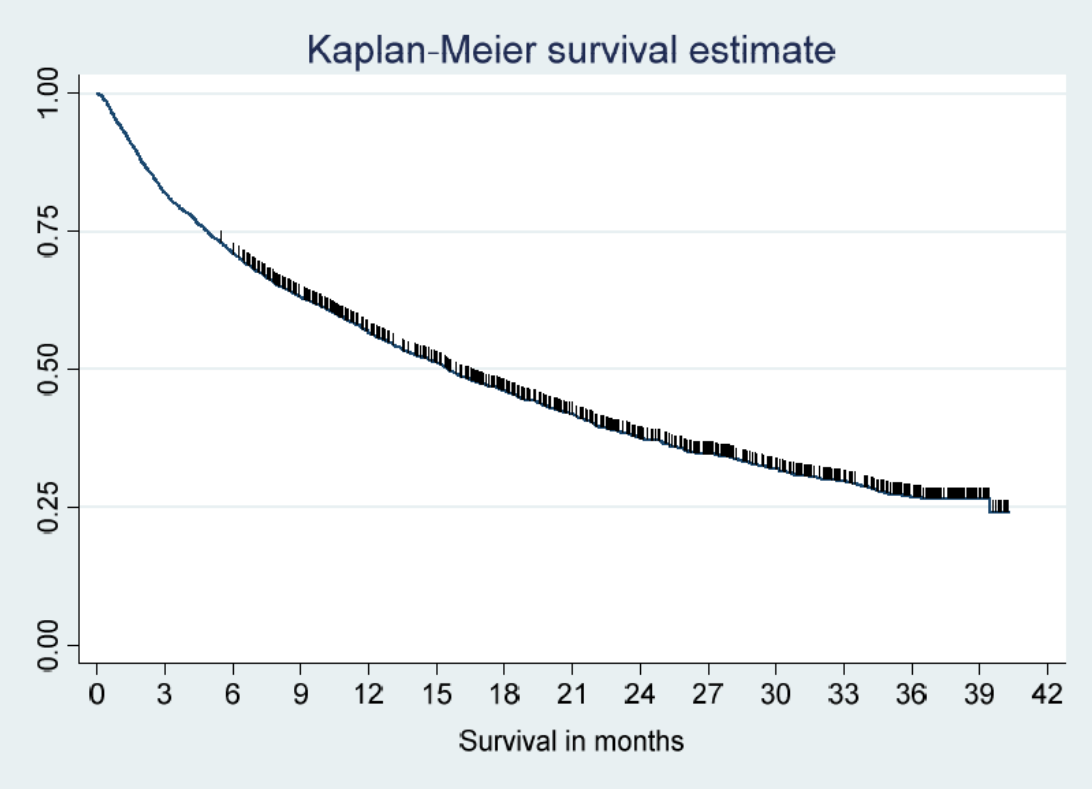


Source: Figure 3 of the daratumumab monotherapy SACT report (2)

Table 15. Number of patients at risk, by quarterly breakpoints- Treatment duration

Time intervals (months)	0-36	3-36	6-36	9-36	12-36	15-36	18-36	21-36	24-36	27-36	30-36	33-36	36
Number at risk	2,300	1,379	847	584	440	332	231	165	119	81	54	26	7

Figure 8. Kaplan-Meier overall survival estimate (n=2,300) : daratumumab monotherapy



Source: Figure 4 of the daratumumab monotherapy SACT report (2)

Table 16. Number of patients at risk, by quarterly breakpoints- Overall survival

Time intervals (months)	0-42	3-42	6-42	9-42	12-42	15-42	18-42	21-42	24-42	27-42	30-42	33-42	36-42	39-42
Number at risk	2,300	1,884	1,631	1,356	1,111	964	783	611	460	346	249	174	96	20

A11. Please clarify the relationship between Table 24 and 25 in the CS. Why is the total in Table 24 (distributions of first treatment after IsaPd) greater than the total in Table 25 (distributions of further lines of therapy after IsaPd) for the CDF, but equal for EAMS?

The reported data were taken from the IsaPd CDF SACT report (1) as provided by NHS Digital, provided in the reference pack.

Some patients in the cohort will have received more than one subsequent therapy. Table 17 (from CS Document B, Table 24 [Table 8 and Table 10 in SACT report, for CDF and EAMS cohort, respectively]), provides the first treatments prescribed after a patient's last IsaPd cycle in SACT. Subsequent therapies could be related to a second primary tumour. Table 18 (from CS Document B, Table 25 [Table 9 and Table 11 in SACT report, for CDF and EAMS cohort, respectively]), provides the distribution of further lines of therapies prescribed after a patient's last IsaPd cycle in SACT. The data reported in Table 17 and Table 18 do not relate to the number of patients that received a particular regimen but rather, the number of instances that the regimen was prescribed.

The Company note a reporting error in Table 25 of the CS Document B. There was an error in the data cited for the distribution of further lines of therapy following a patient's last IsaPd cycle in Table 25 of the CS Document B. A corrected version aligned with the SACT report is provided in Table 18 (below). The company confirm there is no impact on the model.

Table 17. Distribution of first treatments prescribed after a patient's last IsaPd cycle (from CS Document B, Table 24)

Regimen	CDF		EAMS	
	Number of subsequent treatments	%	Number of subsequent treatments	%
Bortezomib + panobinostat	46	46	12	57
Belantamab mafodotin	10	10	3	14
Melphalan	7	7	1	5
Cyclophosphamide	6	6	–	–
Trial unspecified	5	5	2	10
Bortezomib	4	4	–	–
Melphalan + thalidomide	4	4	1	5
Bortezomib + melphalan	3	3	–	–
Bendamustine + thalidomide	2	2	–	–
Cyclophosphamide + thalidomide	2	2	–	–
Pomalidomide	2	2	–	–
Bendamustine	1	1	–	–
Bortezomib + cisplatin + cyclophosphamide + doxorubicin + etoposide + thalidomide	1	1	–	–
Bortezomib + doxorubicin	1	1	–	–
Carfilzomib	1	1	–	–

Regimen	CDF		EAMS	
	Number of subsequent treatments	%	Number of subsequent treatments	%
Carmustine + cytarabine + etoposide + melphalan + rituximab	1	1	–	–
Cisplatin + cytarabine + etoposide	1	1	–	–
Cyclophosphamide + pomalidomide	1	1	–	–
Daratumumab	1	1	–	–
Etoposide + idarubicin + thalidomide	1	1	–	–
Idarubicin	1	1	–	–
Bortezomib + selinexor	–	–	1	5
Cisplatin + cyclophosphamide + doxorubicin + etoposide + thalidomide	–	–	1	5
Thalidomide	–	–	1	5
Total	**101**	**100%**	**22**	**100%**

Source: SACT report (2022) (1).
Abbreviations: CDF, Cancer Drugs Fund; EAMS Early Access to Medicines Scheme; SACT, Systemic Anti-Cancer Therapy.

Table 18. Distribution of further lines of therapy following a patient's last IsaPd cycle (corrected Table 25 from CS Document B)

Regimen	CDF		EAMS	
	Number of subsequent treatments	%	Number of subsequent treatments	%
Belantamab mafodotin	5	5	1	5
Cyclophosphamide	5	5	-	-
Cyclophosphamide + thalidomide	2	2	-	-
Bendamustine	2	2	-	-
Carfilzomib	1	1	1	5
Cyclophosphamide + doxorubicin + vincristine	1	1	-	-
Venetoclax	1	1	-	-
Melphalan + thalidomide	1	1	-	-
Bortezomib + Panobinostat	1	1	-	-
Etoposide + idarubicin + thalidomide	1	1	-	-
Melphalan	1	1	1	5
Trial unspecified	–	–	-	-
Cisplatin + cyclophosphamide + doxorubicin + etoposide + thalidomide	–	–	-	-
Thalidomide	–	–	-	-

Regimen	CDF		EAMS	
	Number of subsequent treatments	%	Number of subsequent treatments	%
Bortezomib + Selinexor	–	–	1	5
Bendamustine +thalidomide	-	-	2	9
MUK 12 Trial			1	5
Total number of subsequent treatments	**21**	**100%**	**7**	**100%**

Source: SACT report (2022) (1).
Abbreviations: CDF, Cancer Drugs Fund; EAMS Early Access to Medicines Scheme; SACT, Systemic Anti-Cancer Therapy.

A12. Please clarify the interval between EQ-5D-5L questionnaires being administered in ICARIA-MM.

In ICARIA-MM trial, EQ-5D-5L questionnaires were administered on Day 1 of Cycle 1, Day 1 of subsequent cycles, end of treatment (30 days after last study treatment administration), and in the post-treatment follow-up period (60 ±5 days after last study treatment administration and every 3 months after last study treatment administration). Cycle duration was 28 days, and Day 1 of Cycle 1 refers to the day the patient received the first study treatment administration. Refer also to the schedule of activities in the CSR ("Table 2 "Study assessment flowchart") (5).

A13. Clarify apparent discrepancies between the reported frequency of AEs between the company's original submission and the frequencies in the new submission. Whilst some change is anticipated due to more mature data it appears that the rate of anaemia in Pd patients has fallen from 1.7% in the original submission to zero in the latest submission. This should not occur as there had been previous events observed. Similarly, (1) asthenia now is zero for IsaPd and Pd yet was positive for IsaPd and Pd in the previous submission, (2) diarrhoea is now zero for IsaPd but was positive previously, (3) hypokalaemia is now zero for IsaPd but was positive previously, (4) hypotension is now zero for Pd but was positive previously and (5) septic shock is now zero for Pd but was positive previously.

The model considers the effects of adverse events (AEs) on costs and health-related quality of life (HRQoL). Only Grade 3 or higher AEs with an incidence of 5% or more for any comparator were considered in the economic model since AEs not meeting this criterion are unlikely to have any material impact on cost-effectiveness. This explains why the AEs highlighted above are 0% or not included in the current model, since the proportion of patients experiencing the AE has fallen below the % incidence considered for inclusion in the model across any comparator. However, it does not imply that the AE rates themselves have fallen between the two data cuts. The AEs seen in the 4th line *safety population (n=51 for IsaPd, n=58 for Pd)* in the updated data cut are provided in response to A15 (Table 23).

Probabilities of AEs for patients receiving IsaPd or Pd treatment in the model were based on patients receiving 4th line treatment in ICARIA-MM (Table 20) and used the *total 4th line population in each arm (n=52 for IsaPd, n=58 for Pd).*

A14. The costs associated with AEs in Table 52 do not match those in Table 33, for example nausea is missing from Table 52. Please provide updated tables.

Thank you for bringing this to our attention. Table 19 presents an updated list of AE costs which include hypokalemia and nausea, and Table 20 presents AE rates as presented in the CS.

Table 19. Adverse event costs [update to CS Table 52]

Adverse event	Estimated cost	Reference
Acute kidney injury	£4,875.27	NHS reference costs 2020/21, Weighted average of: LA07H, LA07J, LA07K (39)
Anaemia	£799.71	NHS reference costs 2020/21, Weighted average of: SA04G, SA04H, SA04I, SA04J, SA04K, SA04L (39)
Fatigue	£774.11	Assumed equal to asthenia in TA783, inflated to 2022(40)
Febrile neutropenia	£7125.94	TA783, inflated to 2022 (40)
Hypercalcaemia	£4,002.42	NHS reference costs 2020/21, Weighted average of: Elective inpatient: Weighted average KC05G, KC05H. Fluid or Electrolyte Disorders, with Interventions, with CC Score 5+, 0-4" and "Non elective short stay: Weighted average KC05G, KC05H. Fluid or Electrolyte Disorders, with Interventions, with CC Score 5+, 0-4" (39)
Hypokalemia	£732.20	NHS reference costs 2020/21, Weighted average of: Elective inpatient: Weighted average KC05J, KC05K, KC05L, KC05M, KC05N. Fluid or Electrolyte Disorders, without Interventions, with CC Score 10+, 7-9, 4-6, 2-3, 0-1" and "NON ELECTIVE SHORT STAY: Weighted average KC05J, KC05K, KC05L, KC05M, KC05N. Fluid or Electrolyte Disorders, without Interventions, with CC Score 10+, 7-9, 4-6, 2-3, 0-1 (39)
Lower respiratory tract infection	£1,858.27	NHS reference costs 2020/21, Weighted average of: Elective inpatient: DZ22K, DZ22L, DZ22M, DZ22N, DZ22P, DZ22Q. Unspecified acute lower respiratory infection, Non-elective short stay: DZ22K, DZ22L, DZ22M, DZ22N, DZ22P, DZ22Q. Unspecified acute lower respiratory infection, and Non-elective long stay: DZ22K, DZ22L, DZ22M, DZ22N, DZ22P, DZ22Q. Unspecified acute lower respiratory infection (39)
Lymphopenia	£928.09	NHS reference costs 2020/21, Weighted average of: SA08G, SA08H, SA08J (39)
Nausea	£774.11	Assumed equal to the cost of asthenia in TA783 (40).
Neutropenia	£928.09	NHS reference costs 2020/21, Weighted average of: SA08G, SA08H, SA08J (39)
Pneumonia	£844.74	NHS reference costs 2020/21, Weighted average of: DZ11K, DZ11L, DZ11M, DZ11N, DZ11P, DZ11Q, DZ11R, DZ11S, DZ11T, DZ11U, DZ11V (39)
Thrombocytopenia	£1,150.97	NHS reference costs 2020/21, Weighted average of: SA12G, SA12H, SA12J, SA12K (39)

Abbreviations: NHS, National Health Service.A15.

Table 20. Proportion of patients with grade ≥3 AEs in ≥5% incidence reported for any comparator [Update to CS Table 33]

Adverse event	IsaPd 4th line†	Pd 4th line†	Isatuximab subcutaneous formulation (scenario)†	Daratumumab monotherapy (40)
Acute kidney injury	3.8%	5.2%	0%	1.5%
Anaemia	0%	0%	10.0%	13.1%
Fatigue	5.8%	0%	0%	0.8%
Febrile neutropenia	13.5%	6.9%	20.0%	1.2%
Hypercalcaemia	1.9%	5.2%	0%	0%
Hypokalemia	0%	0%	0%	0.4%
Lower respiratory tract infection	7.7%	0%	0%	1.5%
Lymphopenia	0%	0%	0%	5.0%
Nausea	0%	0%	0%	0.4%
Neutropenia	46.2%	32.8%	70.0%	13.1%
Pneumonia	21.2%	24.1%	0%	2.7%
Thrombocytopenia	9.6%	10.3%	0%	13.8%

†Internal company analysis of the total 4th line population.
Abbreviations: AE, adverse event; Dara, daratumumab; IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone.

A15. Please provide a detailed summary of safety outcomes from ICARIA-MM.

Safety population

Safety data are summarised in this response for the data cut-off date reported in TA658 (22 November 2018) and at the data cut-off reported in the current submission (22 August 2022).

An overview of treatment emergent adverse events (TEAEs) in the intention to treat (ITT) safety population for ICARIA-MM is provided in Table 21.

A summary of all grade TEAEs by primary System Organ Class (SOC) and preferred term (PT) is presented in Table 22. (A summary of all grade TEAEs by preferred term (PT) was also presented in Appendix M of the CS, Section M.4).

With 3 additional years of follow-up, the overall safety profile remains consistent with what was reported in the previous submission (cut-off date: 22 November 2018). The addition of isatuximab to Pd did not add substantial safety concerns. While Grade 3-4 TEAEs were reported more frequently in the IsaPd arm than in the Pd arm (88.8% versus 74.5%, compared with 84.9% versus 69.1% in the previous submission), the incidence of Grade 5 (fatal) TEAEs was similar in both arms (9.9% versus 10.7%, compared with 7.9% and 9.4% in the IsaPd and Pd arms, respectively in the previous submission). A difference of 12.6% higher incidence of serious TEAEs was observed in the IsaPd arm than in the Pd arm (73.7% versus 61.1%), while there was 8.1% difference at the time of the previous submission (61.8% versus 53.7%); after adjustment for the longer treatment duration in the IsaPd arm, however, the serious TEAE incidence rates were similar in the IsaPd and Pd arms (1.04 versus 0.95 incidence rates per patient-year while it was 1.36 and 1.30 incidence

rates per patient-year, respectively at the first CSR). Definitive treatment discontinuation due to TEAEs occurred at a similar rate in both treatment arms (12.5% in the IsaPd arm and 14.8% in the Pd arm).

Table 21. Overview of TEAEs (safety population ICARIA-MM)

	TA658		ID4067	
Data cut-off date	22-Nov-2018		**22-Aug-2022**	
Treatment arm	**Pd (N=149)**	**IsaPd (N=152)**	**Pd (N=149)**	**IsaPd (N=152)**
Patients with any TEAE	146 (98.0)	151 (99.3)	146 (98.0)	151 (99.3)
Patients with any Grade ≥ 3 TEAE	105 (70.5)	132 (86.8)	113 (75.8)	138 (90.8)
Patients with any Grade 3-4 TEAE	103 (69.1)	129 (84.9)	111 (74.5)	135 (88.8)
Patients with any Grade 5 TEAE	14 (9.4)	12 (7.9)	16 (10.7)	15 (9.9)
Patients with any treatment emergent SAE†	80 (53.7)	94 (61.8)	91 (61.1)	112 (73.7)
Patients with any TEAE leading to definitive treatment discontinuation	19 (12.8)	11 (7.2)	22 (14.8)	19 (12.5)
Patients with any TEAE leading to premature discontinuation of:				
isatuximab	N/A	4 (2.6)	N/A	4 (2.6)
pomalidomide	0	8 (5.3)	0	8 (5.3)
dexamethasone	2 (1.3)	2 (1.3)	4 (2.7)	7 (4.6)
Patients with any AESI‡	1 (0.7)	10 (6.6)	1 (0.7)	14 (9.2)
Patients with any IR of grade ≥ 3	0	4 (2.6)	0	4 (2.6)
Patients with any treatment-related TEAE¶ (any grade)	119 (79.9)	138 (90.8)	120 (80.5)	139 (91.4)
Patients with any treatment-related Grade ≥ 3 TEAE	71 (47.7)	109 (71.7)	75 (50.3)	115 (75.7)
Patients with any serious treatment-related TEAE	24 (16.1)	54 (35.5)	30 (20.1)	61 (40.1)

†TEAEs with a start date before the operational cut-off date and becoming serious after the operational cutoff 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.

Table 22. ICARIA-MM safety outcomes – TEAEs[†] by SOC and PT[‡] (ITT safety population)

	TA658				ID4067			
Data cut-off date	22-Nov-18				22-Aug-2022			
Event n (%)[d]	Pd (N=149)		IsaPd (N=152)		Pd (N=149)		IsaPd (N=152)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any class	146 (98.0)	105 (70.5)	151 (99.3)	132 (86.8)	146 (98.0)	113 (75.8)	151 (99.3)	138 (90.8)
Infections and infestations	96 (64.4)	45 (30.2)	123 (80.9)	65 (42.8)	103 (69.1)	57 (38.3)	126 (82.9	80 (52.6)
Pneumonia	26 (17.4)	23 (15.4)	31 (20.4)	25 (16.4)	38 (25.5)	31 (20.8)	42 (27.6)	35 (23.0)
Upper respiratory tract infection	26 (17.4)	1 (0.7)	43 (28.3)	5 (3.3)	31 (20.8)	4 (2.7)	54 (35.5)	5 (3.3)
Bronchitis	13 (8.7)	1 (0.7)	36 (23.7)	5 (3.3)	17 (11.4)	1 (0.7)	41 (27.0)	8 (5.3)
Urinary tract infection	14 (9.4)	2 (1.3)	15 (9.9)	7 (4.6)	14 (9.4)	2 (1.3)	19 (12.5)	8 (5.3)
Nasopharyngitis	7 (4.7)	0	14 (9.2)	0	10 (6.7)	0	23 (15.1)	0
Lower respiratory tract infection	8 (5.4)	4 (2.7)	8 (5.3)	5 (3.3)	9 (6.0)	4 (2.7)	12 (7.9)	8 (5.3)
Influenza	8 (5.4)	1 (0.7)	9 (5.9)	4 (2.6)	8 (5.4)	1 (0.7)	12 (7.9)	5 (3.3)
Oral herpes	-[†]	-[†]	-[†]	-[†]	3 (2.0)	0	10 (6.6)	0
Respiratory tract infection	-[†]	-[†]	-[†]	-[†]	7 (4.7)	2 (1.3)	8 (5.3)	2 (1.3)
Blood and lymphatic system disorders	65 (43.6)	60 (40.3)	89 (58.6)	87 (57.2)	68 (45.6)	63 (42.3)	97 (63.8)	95 (62.5)
Neutropenia	50 (33.6)	48 (32.2)	71 (46.7)	70 (46.1)	54 (36.2)	52 (34.9)	79 (52.0)	77 (50.7)
Thrombocytopenia	18 (12.1)	18 (12.1)	19 (12.5)	18 (11.8)	18 (12.1)	18 (12.1)	21 (13.8)	20 (13.2)
Febrile neutropenia	3 (2.0)	3 (2.0)	18 (11.8)	18 (11.8)	5 (3.4)	5 (3.4)	18 (11.8)	18 (11.8)
Anaemia	-[†]	-[†]	-[†]	-[†]	2 (1.3)	1 (0.7)	8 (5.3)	7 (4.6)
Metabolism and nutrition disorders	20 (13.4)	8 (5.4)	28 (18.4)	13 (8.6)	22 (14.8)	8 (5.4)	37 (24.3)	15 (9.9)
Decreased appetite	7 (4.7)	1 (0.7)	15 (9.9)	2 (1.3)	8 (5.4)	1 (0.7)	18 (11.8)	2 (1.3)
Psychiatric disorders	29 (19.5)	4 (2.7)	26 (17.1)	4 (2.6)	33 (22.1)	6 (4.0)	31 (20.4)	6 (3.9)
Insomnia	12 (8.1)	1 (0.7)	13 (8.6)	1 (0.7)	14 (9.4)	3 (2.0)	15 (9.9)	2 (1.3)

	TA658				ID4067			
Data cut-off date	22-Nov-18				22-Aug-2022			
Event n (%)[d]	Pd (N=149)		IsaPd (N=152)		Pd (N=149)		IsaPd (N=152)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Nervous system disorders	43 (28.9)	8 (5.4)	62 (40.8)	12 (7.9)	49 (32.9)	10 (6.7)	68 (44.7)	14 (9.2)
Peripheral sensory neuropathy	9 (6.0)	0	11 (7.2)	1 (0.7)	11 (7.4)	0	18 (11.8)	1 (0.7)
Headache	8 (5.4)	0	15 (9.9)	0	9 (6.0)	0	16 (10.5)	1 (0.7)
Tremor	6 (4.0)	0	12 (7.9)	3 (2.0)	7 (4.7)	1 (0.7)	13 (8.6)	3 (2.0)
Dizziness	4 (2.7)	0	8 (5.3)	0	5 (3.4)	0	10 (6.6)	0
Vascular disorders	17 (11.4)	6 (4.0)	23 (15.1)	4 (2.6)	19 (12.8)	7 (4.7)	28 (18.4)	7 (4.6)
Hypertension	8 (5.4)	3 (2.0)	7 (4.6)	2 (1.3)	8 (5.4)	3 (2.0)	11 (7.2)	5 (3.3)
Respiratory, thoracic and mediastinal disorders	48 (32.2)	10 (6.7)	62 (40.8)	14 (9.2)	50 (33.6)	10 (6.7)	69 (45.4)	14 (9.2)
Dyspnoea	15 (10.1)	2 (1.3)	23 (15.1)	6 (3.9)	15 (10.1)	2 (1.3)	25 (16.4)	7 (4.6)
Cough	11 (7.4)	1 (0.7)	14 (9.2)	0	12 (8.1)	1 (0.7)	14 (9.2)	0
Oropharyngeal pain	3 (2.0)	0	8 (5.3)	0	4 (2.7)	0	12 (7.9)	0
Productive cough	-[†]	-[†]	-[†]	-[†]	3 (2.0)	0	8 (5.3)	0
Gastrointestinal disorders	74 (49.7)	3 (2.0)	81 (53.3)	9 (5.9)	81 (51.4)	5 (3.4)	86 (56.6)	13 (8.6)
Diarrhoea	29 (19.5)	1 (0.7)	39 (25.7)	3 (2.0)	33 (22.1)	2 (1.3)	48 (31.6)	3 (2.0)
Constipation	26 (17.4)	0	24 (15.8)	0	30 (20.1)	0	27 (17.8)	0
Nausea	14 (9.4)	0	23 (15.1)	0	14 (9.4)	0	24 (15.8)	0
Vomiting	5 (3.4)	0	18 (11.8)	2 (1.3)	6 (4.0)	0	20 (13.2)	2 (1.3)
Stomatitis	4 (2.7)	0	10 (6.6)	1 (0.7)	4 (2.7)	0	10 (6.6)	1 (0.7)
Abdominal pain	-[†]	-[†]	-[†]	-[†]	6 (4.0)	0	8 (5.3)	0
Skin and subcutaneous tissue disorders	36 (24.2)	0	39 (25.7)	2 (1.3)	37 (24.8)	1 (0.7)	50 (32.9)	3 (2.0)
Pruritus	9 (6.0)	0	5 (3.3)	0	11 (7.4)	0	9 (5.9)	0

	TA658				ID4067			
Data cut-off date	22-Nov-18				22-Aug-2022			
Event n (%)[d]	Pd (N=149)		IsaPd (N=152)		Pd (N=149)		IsaPd (N=152)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Rash	8 (5.4)	0	5 (3.3)	0	8 (5.4)	0	11 (7.2)	0
Musculoskeletal and connective tissue disorders	74 (49.7)	8 (5.4)	86 (56.6)	12 (7.9)	78 (52.3)	9 (6.0)	97 (63.8)	16 (10.5)
Back pain	22 (14.8)	2 (1.3)	25 (16.4)	3 (2.0)	25 (16.8)	2 (1.3)	30 (19.7)	4 (2.6)
Arthralgia	13 (8.7)	1 (0.7)	16 (10.5)	4 (2.6)	20 (13.4)	1 (0.7)	22 (14.5)	3 (2.0)[‡]
Muscle spasms	15 (10.1)	0	14 (9.2)	0	16 (10.7)	0	17 (11.2)	1 (0.7)
Musculoskeletal chest pain	7 (4.7)	0	13 (8.6)	0	7 (4.7)	0	15 (9.9)	0
Muscular weakness	7 (4.7)	0	11 (7.2)	1 (0.7)	8 (5.4)	0	14 (9.2)	1 (0.7)
Bone pain	8 (5.4)	2 (1.3)	12 (7.9)	1 (0.7)	13 (8.7)	2 (1.3)	13 (8.6)	2 (1.3)
Pathological fracture	8 (5.4)	3 (2.0)	9 (5.9)	3 (2.0)	9 (6.0)	4 (2.7)	13 (8.6)	5 (3.3)
Myalgia	5 (3.4)	0	10 (6.6)	0	5 (3.4)	0	12 (7.9)	0
Renal and urinary disorders	23 (15.4)	12 (8.1)	18 (11.8)	9 (5.9)	23 (15.4)	12 (8.1)	22 (14.5)	10 (6.6)
Acute kidney injury	8 (5.4)	6 (4.0)	7 (4.6)	4 (2.6)	8 (5.4)	6 (4.0)	9 (5.9)	4 (2.6)
General disorders and administration site conditions	89 (59.7)	18 (12.1)	82 (53.9)	23 (15.1)	91 (61.1)	20 (13.4)	91 (59.9)	29 (19.1)
Fatigue	32 (21.5)	0	26 (17.1)	6 (3.9)	32 (21.5)	0	30 (19.7)	6 (3.9)
Oedema peripheral	16 (10.7)	0	20 (13.2)	1 (0.7)	18 (12.1)	0	30 (19.7)	2 (1.3)
Pyrexia	21 (14.1)	2 (1.3)	22 (14.5)	2 (1.3)	21 (14.1)	2 (1.3)	25 (16.4)	4 (2.6)
Asthenia	27 (18.1)	4 (2.7)	23 (15.1)	5 (3.3)	29 (19.5)	4 (2.7)	24 (15.8)	5 (3.3)
Disease progression	8 (5.4)	8 (5.4)	8 (5.3)	8 (5.3)	9 (6.0)	9 (6.0)	10 (6.6)	10 (6.6)
Influenza like illness	-[†]	-[†]	-[†]	-[†]	5 (3.4)	0	8 (5.3)	1 (0.7)
Investigations	10 (6.7)	2 (1.3)	17 (11.2)	5 (3.3)	15 (10.1)	4 (2.7)	22 (14.5)	5 (3.3)
Weight decreased	2 (1.3)	0	10 (6.6)	0	2 (1.3)	0	10 (6.6)	0

	TA658				ID4067			
Data cut-off date	22-Nov-18				22-Aug-2022			
Event n (%)[d]	Pd (N=149)		IsaPd (N=152)		Pd (N=149)		IsaPd (N=152)	
	All grades	Grade ≥3	All grades	Grade ≥3	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)	19 (12.8)	3 (2.0)	77 (50.7)	9 (5.9)
Infusion related reaction	2 (1.3)	0	56 (36.8)	4 (2.6)	2 (1.3)	0	57 (37.5)	4 (2.6)
Fall	8 (5.4)	1 (0.7)	8 (5.3)	0	9 (6.0)	1 (0.7)	12 (7.9)	0
Eye disorders	-†	-†	-†	-†	21 (14.1)	6 (4.0)	24 (15.8)	7 (4.6)
Cataract	-†	-†	-†	-†	11 (7.4)	4 (2.7)	15 (9.9)	7 (4.6)
Cardiac disorders	-†	-†	-†	-†	9 (6.0)	5 (3.4)	34 (22.4)	12 (7.9)
Atrial fibrillation	-†	-†	-†	-†	3 (2.0)	1 (0.7)	10 (6.6)	3 (2.0)

Source: Sanofi, Clinical study report, data on file (2022) (5).†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 (22-Aug-2022 data cut).
† Data not reported in TA658 as incidence <5%
ǂ 1 Grade 3 event was downgraded to Grade 2 severity after first data cut-off
Abbreviations: IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; MedDRA, Medical Dictionary for Regulatory Activities; MM, multiple myeloma

Safety population: 4th line subgroup

Data from the safety population in the 4th line subgroup for this submission were from data cut-off date 14 March 2022.

Table 29 reporting the overview of TEAEs from the 4th line safety population of ICARIA-MM (3) has been updated to include the data reported in the previous submission (TA658) (41).

In addition, a summary of all grade TEAEs by primary system organ class (SOC) (only SOC where preferred term [PT] ≥5% in any treatment arm) and PT ≥5% is presented in Table 23 (42).

Table 29. Overview of TEAEs (safety population 4th line subgroup)

	TA658		ID4067	
Data cut-off date	**22-Nov-2018**		**14-Mar-2022**	
Treatment arm	**Pd (N=58)**	**IsaPd (N=51)**	**Pd (N=58)**	**IsaPd (N=51)**
Patients with any TEAE	57 (98.3)	51 (100)	57 (98.3)	51 (100)
Patients with any Grade ≥ 3 TEAE	40 (69.0)	43 (84.3)	43 (74.1)	46 (90.2)
Patients with any Grade 3-4 TEAE	39 (67.2)	42 (82.4)	42 (72.4)	45 (88.2)
Patients with any Grade 5 TEAE	5 (8.6)	4 (7.8)	6 (10.3)	5 (9.8)
Patients with any treatment emergent SAE†	31 (53.4)	33 (64.7)	34 (58.6)	41 (80.4)
Patients with any TEAE leading to definitive treatment discontinuation	10 (17.2)	4 (7.8)	11 (19.0)	7 (13.7)
Patients with any TEAE leading to premature discontinuation of:				
isatuximab	N/A	1 (2.0)	NA	1 (2.0)
pomalidomide	0	2 (3.9)	0	2 (3.9)
dexamethasone	1 (1.7)	1 (2.0)	2 (3.4)	2 (3.9)
Patients with any AESI‡	0	4 (7.8)	0	5 (9.8)
Patients with any IR of grade ≥ 3	0	1 (2.0)	0	1 (2.0)
Patients with any treatment-related TEAE¶ (any grade)	1 (1.7)	1 (2.0)	45 (77.6)	45 (88.2)
Patients with any treatment-related grade ≥ 3 TEAE	27 (46.6)	33 (64.7)	29 (50.0)	36 (70.6)
Patients with any serious treatment-related TEAE	11 (19.0)	17 (33.3)	13 (22.4)	20 (39.2)

Source: Sanofi, Clinical study report fourth-line analysis, data on file (2022) (3).
Notes: † 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
Abbreviations: IsaPd, Isatuximab + pomalidomide + dexamethasone; NA, Not applicable; Pd, pomalidomide + dexamethasone; TEAE, treatment emergent adverse event.

Table 23. TEAEs by primary SOC† and PT (worst grade by patient) – Safety population 4th line subgroup

Data cut-off date: 14 March 2022	Pd (n=58)		IsaPd (n=51)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any class	57 (98.3)	43 (74.1)	51 (100.0)	46 (90.2)
Infections and infestations	37 (63.8)	21 (36.2)	42 (82.4)	28 (54.9)
Bronchitis	4 (6.9)	0	16 (31.4)	2 (3.9)
Upper respiratory tract infection	8 (13.8)	2 (3.4)	16 (31.4)	0
Pneumonia	18 (31.0)	14 (24.1)	13 (25.5)	11 (21.6)
Nasopharyngitis	3 (5.2)	0	10 (19.6)	0
Influenza	2 (3.4)	0	4 (7.8)	1 (2.0)
Lower respiratory tract infection	2 (3.4)	0	4 (7.8)	4 (7.8)
Urinary tract infection	5 (8.6)	1 (1.7)	4 (7.8)	3 (5.9)
Gastroenteritis	2 (3.4)	1 (1.7)	3 (5.9)	0
Oral herpes	1 (1.7)	0	3 (5.9)	0
Respiratory tract infection	5 (8.6)	1 (1.7)	3 (5.9)	2 (3.9)
Rhinitis	1 (1.7)	0	3 (5.9)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.7)	0	4 (7.8)	4 (7.8)
Squamous cell carcinoma of skin	0	0	3 (5.9)	2 (3.9)
Blood and lymphatic system disorders	26 (44.8)	24 (41.4)	28 (54.9)	27 (52.9)
Neutropenia	19 (32.8)	19 (32.8)	25 (49.0)	24 (47.1)
Febrile neutropenia	4 (6.9)	4 (6.9)	7 (13.7)	7 (13.7)
Thrombocytopenia	6 (10.3)	6 (10.3)	5 (9.8)	5 (9.8)
Metabolism and nutrition disorders	8 (13.8)	3 (5.2)	11 (21.6)	3 (5.9)
Decreased appetite	1 (1.7)	0	7 (13.7)	0
Hypercalcaemia	3 (5.2)	3 (5.2)	1 (2.0)	1 (2.0)

Data cut-off date: 14 March 2022	Pd (n=58)		IsaPd (n=51)	
	All grades	Grade ≥3	All grades	Grade ≥3
Psychiatric disorders	12 (20.7)	2 (3.4)	11 (21.6)	2 (3.9)
Insomnia	6 (10.3)	1 (1.7)	6 (11.8)	1 (2.0)
Nervous system disorders	20 (34.5)	4 (6.9)	23 (45.1)	5 (9.8)
Headache	4 (6.9)	0	9 (17.6)	1 (2.0)
Peripheral sensory neuropathy	5 (8.6)	0	6 (11.8)	0
Tremor	2 (3.4)	0	6 (11.8)	2 (3.9)
Eye disorders	7 (12.1)	1 (1.7)	8 (15.7)	2 (3.9)
Cataract	4 (6.9)	1 (1.7)	5 (9.8)	2 (3.9)
Ear and labyrinth disorders	3 (5.2)	0	3 (5.9)	0
Vertigo	1 (1.7)	0	3 (5.9)	0
Vascular disorders	7 (12.1)	3 (5.2)	9 (17.6)	0
Hypertension	1 (1.7)	0	4 (7.8)	0
Hypotension	2 (3.4)	2 (3.4)	3 (5.9)	0
Deep vein thrombosis	3 (5.2)	1 (1.7)	1 (2.0)	0
Respiratory, thoracic and mediastinal disorders	18 (31.0)	3 (5.2)	23 (45.1)	1 (2.0)
Dyspnoea	3 (5.2)	0	9 (17.6)	1 (2.0)
Oropharyngeal pain	0	0	6 (11.8)	0
Productive cough	2 (3.4)	0	6 (11.8)	0
Cough	5 (8.6)	1 (1.7)	5 (9.8)	0
Epistaxis	1 (1.7)	0	3 (5.9)	0
Gastrointestinal disorders	33 (56.9)	2 (3.4)	29 (56.9)	6 (11.8)
Diarrhoea	13 (22.4)	1 (1.7)	16 (31.4)	2 (3.9)
Constipation	10 (17.2)	0	11 (21.6)	0

Data cut-off date: 14 March 2022	Pd (n=58)		IsaPd (n=51)	
	All grades	Grade ≥3	All grades	Grade ≥3
Vomiting	2 (3.4)	0	9 (17.6)	1 (2.0)
Nausea	7 (12.1)	0	8 (15.7)	0
Stomatitis	1 (1.7)	0	4 (7.8)	1 (2.0)
Abdominal distension	1 (1.7)	0	3 (5.9)	0
Abdominal pain	1 (1.7)	0	3 (5.9)	0
Abdominal pain upper	2 (3.4)	0	3 (5.9)	1 (2.0)
Dysphagia	0	0	3 (5.9)	0
Toothache	0	0	3 (5.9)	0
Skin and subcutaneous tissue disorders	11 (19.0)	1 (1.7)	18 (35.3)	1 (2.0)
Erythema	1 (1.7)	0	5 (9.8)	0
Pruritus	2 (3.4)	0	3 (5.9)	0
Rash	3 (5.2)	0	3 (5.9)	0
Musculoskeletal and connective tissue disorders	32 (55.2)	6 (10.3)	38 (74.5)	7 (13.7)
Back pain	11 (19.0)	2 (3.4)	13 (25.5)	2 (3.9)
Arthralgia	8 (13.8)	0	12 (23.5)	2 (3.9)
Muscle spasms	7 (12.1)	0	8 (15.7)	1 (2.0)
Muscular weakness	4 (6.9)	0	6 (11.8)	0
Pathological fracture	6 (10.3)	3 (5.2)	6 (11.8)	1 (2.0)
Musculoskeletal chest pain	2 (3.4)	0	5 (9.8)	0
Pain in extremity	3 (5.2)	0	5 (9.8)	0
Bone pain	6 (10.3)	1 (1.7)	4 (7.8)	1 (2.0)
Myalgia	1 (1.7)	0	3 (5.9)	0
Renal and urinary disorders	7 (12.1)	3 (5.2)	6 (11.8)	3 (5.9)

Data cut-off date: 14 March 2022	Pd (n=58)		IsaPd (n=51)	
	All grades	Grade ≥3	All grades	Grade ≥3
Acute kidney injury	4 (6.9)	3 (5.2)	2 (3.9)	2 (3.9)
Reproductive system and breast disorders	1 (1.7)	0	5 (9.8)	2 (3.9)
Pelvic pain	0	0	3 (5.9)	2 (3.9)
General disorders and administration site conditions	38 (65.5)	10 (17.2)	31 (60.8)	9 (17.6)
Fatigue	11 (19.0)	0	13 (25.5)	3 (5.9)
Oedema peripheral	10 (17.2)	0	11 (21.6)	0
Pyrexia	11 (19.0)	2 (3.4)	9 (17.6)	0
Asthenia	13 (22.4)	2 (3.4)	6 (11.8)	1 (2.0)
Influenza like illness	2 (3.4)	0	4 (7.8)	1 (2.0)
Disease progression	5 (8.6)	5 (8.6)	3 (5.9)	3 (5.9)
Non-cardiac chest pain	0	0	3 (5.9)	0
Peripheral swelling	0	0	3 (5.9)	0
Investigations	6 (10.3)	3 (5.2)	7 (13.7)	1 (2.0)
Weight decreased	0	0	4 (7.8)	0
Injury, poisoning and procedural complications	7 (12.1)	2 (3.4)	25 (49.0)	2 (3.9)
Infusion related reaction	1 (1.7)	0	16 (31.4)	1 (2.0)
Contusion	0	0	3 (5.9)	0
Fall	4 (6.9)	1 (1.7)	3 (5.9)	0

Source: Sanofi. Clinical Study Report – Appendices (4th line subgroup analysis) Table 1.9.2 (42)
Notes: Cut-off date 14 March 2022
MedDRA 24.1
n (%) = number and percentage of patients with at least one TEAE
† Only SOC with PT ≥5% in any treatment arm
Table sorted by SOC internationally agreed order and by decreasing frequency of PT for all grades in IsaPd group
Abbreviations: IsaPd, Isatuximab + pomalidomide + dexamethasone; NA, Not applicable; Pd, pomalidomide + dexamethasone; PT, preferred term; SOC, system organ class; TEAE, treatment emergent adverse event.

Section B: Clarification on cost-effectiveness data

Modelling assumptions and calculations

B1. Priority. In B.3.2.1 it is stated that the patient population has received a median of three lines of prior treatment. Please clarify if this is correct, if so, clarify why a median has been used rather than using a population who have all had three lines of therapy.

This was an error in text and should read: 'The population in the model base case is the subgroup of patients from the ICARIA-MM trial who have received only three prior lines of therapy (4th line).' The population used in the economic analysis and the model base case are those that have had three prior lines of therapy.

B2. Priority. Please clarify when [redacted]

[redacted]

B3. Priority. Please clarify whether the modelling time horizon in the SACT analysis was reduced to 20 years. If not, clarify why there is a large decrease in the number of patients assumed to be in post-progression for IsaPd in the figure in the Comp1 Calc worksheet for the comparison with daratumumab monotherapy.

The mentioned trace figure was previously not accurate past 20 years due to the change in cycle duration at this time point. This has been amended in the revised version of the submission model. Updated base case results have been provided in response to B4.

B4. Priority. The CS (in B.3.5.2.5) states that a total of 17% of patients who received IsaPd in the combined EAMS and CDF cohorts received a subsequent therapy in the SACT dataset. However, It appears that the one-off cost associated with subsequent treatment (cell FW22 in a 'Calc' sheet) is applied to all patients discontinuing treatment regardless of whether they died or progressed. This is shown by the undiscounted costs of subsequent treatments per patient (cell F65 in a 'Calc' sheet) being approximately the same as the estimated costs of a patient receiving subsequent treatments (FW22 in a 'Calc' sheet). Clarify if this was intended. If not intended, please amend the model, if it was intended, then explain the discrepancy between the 17% value observed in SACT, the 100% used in the model and the values of [redacted] **and** [redacted] **which are the sums of F26:F36 and I26:I36 in the 'Costs_PostStudyTherapy' worksheet. Further, please clarify how many patients received further treatment in ICARIA-MM and how this links to the values used in the**

scenario analysis of [redacted] and [redacted] which are the sums of P229:P239 and P240:250 in the 'Scenario_inputs' worksheet.

We thank the EAG for identifying this. In response to this clarification question, an error was identified and corrected for how individual probabilities of receipt of the SACT subsequent therapies were calculated. The previous probabilities were conditional on the denominator population of those who had received a subsequent therapy, instead of the denominator population of those who had discontinued. In essence, this introduced an underlying assumption that all patients who discontinue go on to receive subsequent therapy, which was not intended. This correction is more in-line with what was observed in the IsaPd SACT data, as among those who discontinued in the combined EAMS and CDF cohorts, probability of receipt of at least one subsequent therapy was 31.3%. The updated individual probabilities of receipt derived from the two SACT datasets are shown below (Table 24).

Table 24. Updated individual probabilities of subsequent treatment receipt derived from respective SACT datasets [Update to CS Table 46]

Subsequent Treatment	IsaPd SACT (combined cohort)	Daratumumab SACT
Bendamustine	0.99%	2.1%
Bortezomib	1.31%	0.8%
Bortezomib + panobinostat	19.38%	16.7%
Cyclophosphamide + pomalidomide	0.33%	4.6%
Cyclophosphamide	3.61%	2.8%
Cyclophosphamide + thalidomide	1.31%	1.1%
Lenalidomide	0.00%	0.0%
Melphalan	3.28%	2.3%
Bendamustine + thalidomide	1.31%	1.2%
Pomalidomide	0.66%	49.9%
Belantamab mafodotin	6.24%	0.6%

Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; SACT, systemic anti-cancer therapy.

As the above probabilities are conditional on those who discontinue 4th line treatment, they are applied to all patients who discontinue in the model.

The values used in the scenario analysis for the IsaPd vs Pd comparison evaluating subsequent treatment from ICARIA-MM were calculated by dividing the number of patients who received each subsequent treatment in each arm by the number of patients who were flagged as definitely discontinued in each arm within the ICARIA-MM trial. The data captures all treatments received after discontinuation; this can potentially include several treatments received simultaneously or multiple lines of therapy. Therefore, the probabilities of receipt are estimated with respect to each individual therapy and should not be considered mutually exclusive (i.e., should not necessarily sum to 1). Values used in the calculations for the ICARIA-MM subsequent therapies scenario analysis are shown below (Table 25).

Table 25. Subsequent treatment receipt in ICARIA-MM (used in scenario analysis) [Update to CS Table 47]

Treatment	IsaPd		Pd	
4th line Patients	N=52		N=58	
Item	**Patient**	**Percent**	**Patient**	**Percent**
Discontinued, N	44		56	
Carfilzomib	17	38.6%	16	28.6%
Cyclophosphamide	14	31.8%	18	32.1%
Daratumumab	8	18.2%	23	41.1%
Bortezomib	10	22.7%	13	23.2%
Melphalan	10	22.7%	4	7.1%
Bendamustine	7	15.9%	5	8.9%
Pomalidomide	6	13.6%	6	10.7%
Lenalidomide	6	13.6%	4	7.1%
Doxorubicin	5	11.4%	2	3.6%
Etoposide	4	9.1%	1	1.8%
Belantamab	2	4.5%	2	3.6%

Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone.

Updated Base case cost-effectiveness results

Updated base case results for both comparisons have been presented in response to corrections made for question B4. As can be noted, there is an increase in the base case incremental cost effectiveness ratio (ICER) for the IsaPd vs Pd comparison once the model was updated. This is primarily driven by the adjustment to how the subsequent treatments were applied in the model which were derived from SACT in response to question B4.

IsaPd vs Pd

Results vs Pd are presented in Table 26 for the base case analysis assuming a [redacted] patient access scheme (PAS) discount for isatuximab and list price for all other therapies. Table 27 and Table 28 present the non-reference case analyses vs Pd removing the backbone cost of Pd and assuming a [redacted] discount to the list price of pomalidomide, respectively. Reference and non-reference case analyses vs Pd consider a [redacted] PAS for isatuximab only.

Table 26. Base case results vs Pd

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£182,769

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; Pd, pomalidomide + dexamethasone; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 27. Base case results vs Pd – pomalidomide and dexamethasone backbone cost removed

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£63,721

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; Pd, pomalidomide + dexamethasone; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 28. Base case results vs Pd – generic pomalidomide available†

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£85,868

†Discount of [redacted] of pomalidomide assumed

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; Pd, pomalidomide + dexamethasone; PAS, patient access scheme; QALYs, quality-adjusted life years.

IsaPd vs daratumumab monotherapy

Results vs daratumumab monotherapy are presented in Table 29 for the base case analysis assuming a [redacted] PAS for isatuximab and list price for all other therapies. Table 30 and Table 31 present the non-reference case analyses vs daratumumab monotherapy removing the backbone cost of Pd and assuming a [redacted] discount to the list price of pomalidomide. Reference and non-reference case analyses vs daratumumab monotherapy consider a [redacted] PAS for isatuximab only.

Table 29. Base case results vs daratumumab monotherapy

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Daratumumab	[redacted]	[redacted]	[redacted]	-	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£141,251

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years; WTP, willingness to pay.

Table 30. Base case results vs daratumumab monotherapy – pomalidomide and dexamethasone backbone cost removed

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER (£/QALY)
Daratumumab	[redacted]	[redacted]	[redacted]	-	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£60,957

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years; WTP, willingness to pay.

Table 31. Base case results vs daratumumab monotherapy– generic pomalidomide available†

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER (£/QALY)
Daratumumab	[redacted]	[redacted]	[redacted]	-	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,915

†Discount of [redacted] of pomalidomide assumed
Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years; WTP, willingness to pay.

Probabilistic sensitivity analysis results

Results of PSA of IsaPd vs Pd are presented in Table 32. The average incremental costs over the simulated results were [redacted] and the average incremental QALYs were [redacted], resulting in a probabilistic ICER of £192,673, when considering a PAS discount for isatuximab only.

Table 32. Probabilistic sensitivity analysis results (IsaPd vs Pd)- PAS for isatuximab only

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Pd	[redacted]	[redacted]	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	£192,673

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; Pd, pomalidomide + dexamethasone; PAS, patient access scheme; QALYs, quality-adjusted life years.

Figure 9. Scatter plot of simulations on cost-effectiveness plane (IsaPd vs Pd)

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; PA, probabilistic analysis; Pd, pomalidomide + dexamethasone; WTP, willingness to pay.

Results of PSA of IsaPd vs daratumumab monotherapy are presented in Table 33. The average incremental costs over the simulated results were [redacted] and the average incremental QALYs were [redacted], resulting in a probabilistic ICER of £142,577, when considering a PAS discount for isatuximab only. This is congruent with the deterministic ICER of £141,251 vs daratumumab monotherapy.

Table 33. Probabilistic sensitivity analysis results (IsaPd vs daratumumab monotherapy)- PAS for isatuximab only

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Daratumumab	[redacted]	[redacted]	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	£142,577

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

Figure 10. Scatter plot of simulations on cost-effectiveness plane (IsaPd vs daratumumab monotherapy)

[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; PA, probabilistic analysis; QALY, quality adjusted life year; WTP, willingness to pay.

B5. Priority. Please clarify why the sum of the number of people discontinuing treatment appears to be greater than 1. The impact of this can be seen by the costs of subsequent treatments in cell F65 of a results sheet, for example 'Comp1 Calc', being greater than cell FW22. It may be that the reweighting is greater than 1 as the sum of comp1.pp_tx1 to comp1.pp_tx10 (H2016:H2035) equals 1.028.

This observation is due to a very small estimation error introduced when applying half-cycle correction to a model in which the cycle periodicity changes. Considering the size of the error is quite small in terms of the overall trace (10^{-5}), and that most transitions happen before the point at which the cycle periodicity changes, any impact can be considered minor.

B6. Please clarify why the drug costs for isatuximab and dexamethasone appear to be calculated every 28 days rather than every 14 days and 7 days respectively. Clarify why administration costs for isatuximab appear to be calculated every 7 days rather than every 14 days. The EAG notes that the impact of this possible error will be small and unfavourable to isatuximab.

To avoid difficulties with modelling complex dosing cycles explicitly while also making the model flexible enough to allow for varied medication regimens, some simplifications were made when calculating medication and administration costs.

For medication costs, it was assumed that the full cost of a drug cycle would be assigned to the first week of that cycle. For a drug like isatuximab, which is administered on a 28-day cycle as per the ICARIA-MM protocol, this approach slightly front-loaded the costs to the first week, as medication costs for four model cycles are assigned to the first. While administration costs are also simplified, a different approach is used. Rather than costing an entire drug cycle during its first week, an average cost per week is calculated and applied for each week of a drug cycle.

Upon review of the EAG's question it was felt that having one unified approach for calculating medication and administration costs would be more appropriate, and as such the per-week approach used for administration costs has now also been applied for calculating medication costs in the revised model. While the overall effect of this change is small, it is slightly favourable to the IsaPd arm.

B7. Please clarify how the PSA samples that are referred to as coming from empirical distributions were obtained, for example, those in the 'PA_Bootstraps_Inputs' sheet cells AS15:AT1014. Clarify whether the company checked that there are not large discrepancies between the summary statistics (mean and standard error) of the empirical distributions and the summary statistics from the assumed distribution.

The bootstrapping procedure creates samples of the ICARIA-MM 4th line population by sampling with replacement from each of the trial arms. The size of the trial arms in the samples is configured such that they are the same as observed empirically in the 4th line population (n= 52 for IsaPd, n=58 for Pd). Estimates for model variables are then calculated from these samples, such as curve-fitting parameters for the four outcomes (PFS, PFS-on Tx, TTD and OS), incidence of adverse events, health state utilities, etc.

While the summary statistics of the bootstrapped distribution are generally close to the observed values, given the large number of items being sampled it is not unlikely that some, by chance, may differ from their mean value. Note that some of the sampled inputs, such as those used in the parametric functions, may be transformed before being used.

B8. Please clarify whether there is a need for correlation in the utility values for PFS on IsaPd and PFS on Pd in Table 36. Is it plausible that the PFS on Pd is higher than PFS on IsaPd? This appears to happen 23 times in 1000 looking at columns HC and HH in the 'PA_Bootstraps_Inputs' worksheet.

Columns HC and HH are of EQ-5D-5L utility values for IsaPd and EQ-5D-3L utility values for Pd, respectively. It is therefore not recommended to compare these two columns.

Comparing the two columns with EQ-5D-3L values (columns HH and GX), the utility value for PFS is higher for Pd in 16 of the 1000 bootstrapped sample populations. While we agree that this is unexpected, on average, a higher PFS utility value for Pd in ~2% of the samples is simply reflective of the random sampling process employed when creating the bootstrapped distributions. The two arms are independent random samples, and therefore the distributions of utility values are theoretically independent. However, the estimation procedure utilises both samples, and as a result, there may be some correlation introduced via the procedure between IsaPd and Pd. To the extent that there is any correlation, it appropriately reflects that introduced by the estimation procedure.

B9. Please clarify whether the AE profile for IsaPd was intended to be the same in both the base case analysis and the exploratory analysis compared with daratumumab monotherapy. It appears that variable 'comp1.ae3' (cell F2348 in the 'Variables' worksheet) is zero in the exploratory analysis but has a value of 3.8% (as reported in Table 33) in the primary analysis. Setting these values equal does not appear to result in equal AE costs for IsaPd in the two analyses. Please check the model and amend as appropriate.

The AE profile is the same between the two analyses, however, the inclusion criteria for which AEs are modelled (i.e., ≥5% incidence in any comparator) is partly determined by the comparators included in the analysis. In this case, acute kidney injury is modelled in the primary analysis vs Pd because the incidence for acute kidney injury in Pd meets the ≥5% threshold criteria (3.8% for IsaPd and 5.2% for Pd), while it is not included in the exploratory analysis vs daratumumab monotherapy as there is no active comparator with incidence for this AE ≥5%.

Survival extrapolation

B10. Priority. Please clarify how the empirical hazard was computed (for example, CS Figure 12 and Figure 29 B). Please provide an example code for computing the hazard rate. The KM plot from Figure 29 A shows that there are death events between 20-30

months, however, the hazard rate plot in Figure 29 B shows a constant hazard rate for this period. Please explain this discrepancy.

There is no discrepancy here as the hazard rate, while appearing constant between the 20 to 30-month period in Figure 29B, is also non-zero during this time and thus representative of the KM plot.

B11. Priority. Please provide plots showing the empirical/unsmoothed hazard functions (using pehaz() with default width from the muhaz package in R) and smoothed hazard functions (using muhaz() from the muhaz package in R) for all the time-to-event outcomes which require extrapolation.

The requested smoothed and unsmoothed hazard functions for all evaluated ICARIA-MM and SACT time-to-event outcomes have been provided below along with the numbers at risk (Figure 11 - Figure 22).

Figure 11. IsaPd OS, ICARIA-MM

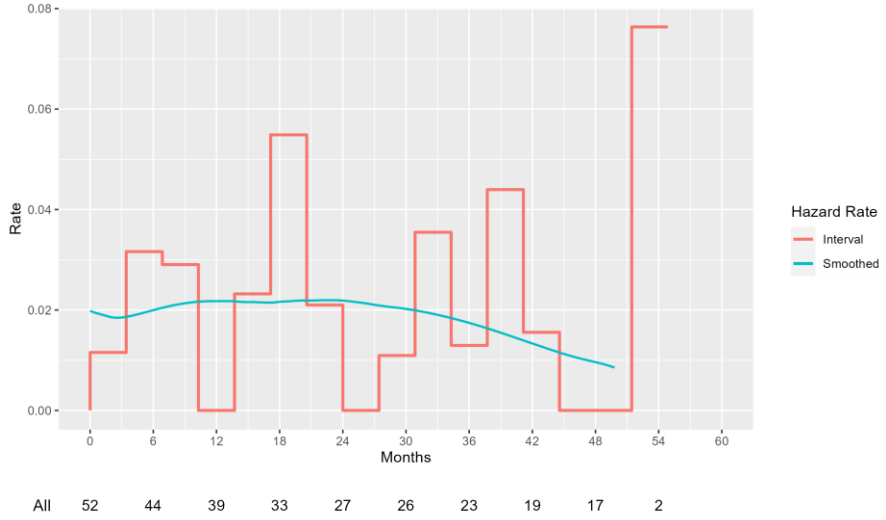


Figure 12. Pd OS, ICARIA-MM

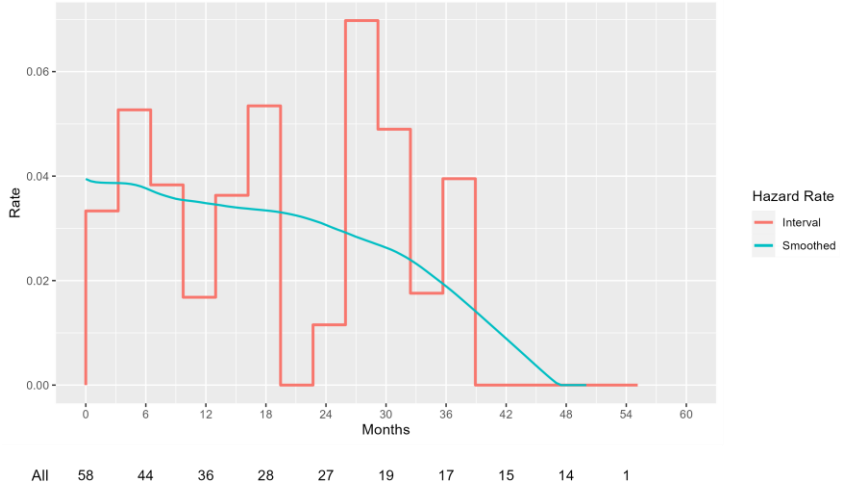


Figure 13. IsaPd PFS, ICARIA-MM

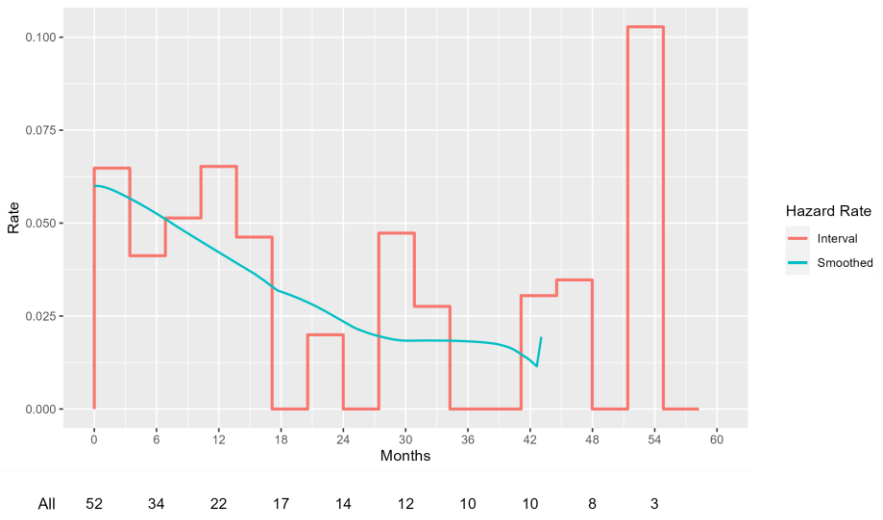


Figure 14. Pd PFS, ICARIA-MM

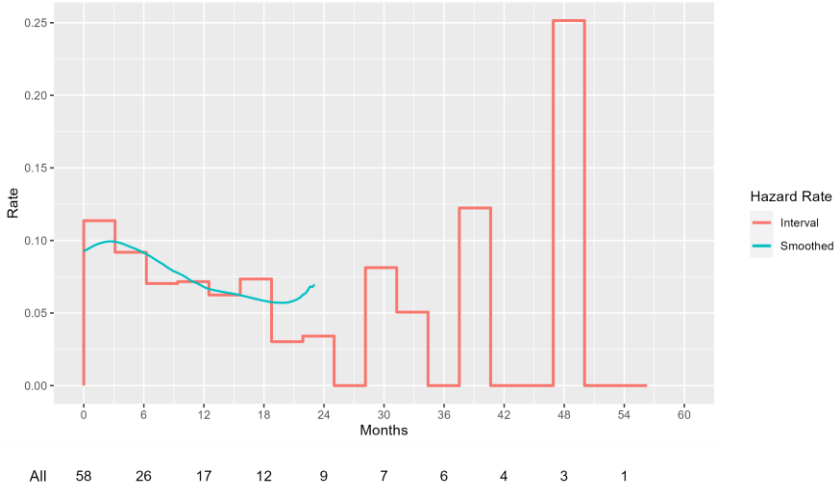


Figure 15. IsaPd PFS On-Tx, ICARIA-MM

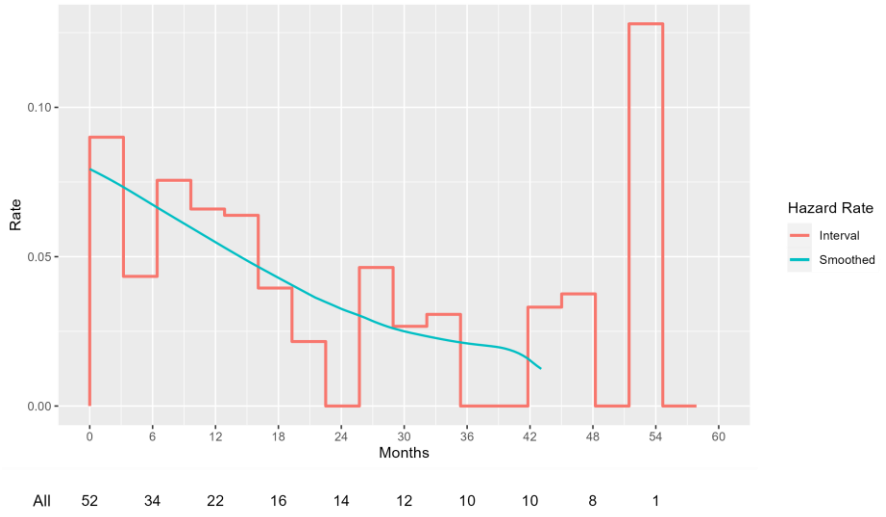


Figure 16. Pd PFS On-Tx, ICARIA-MM

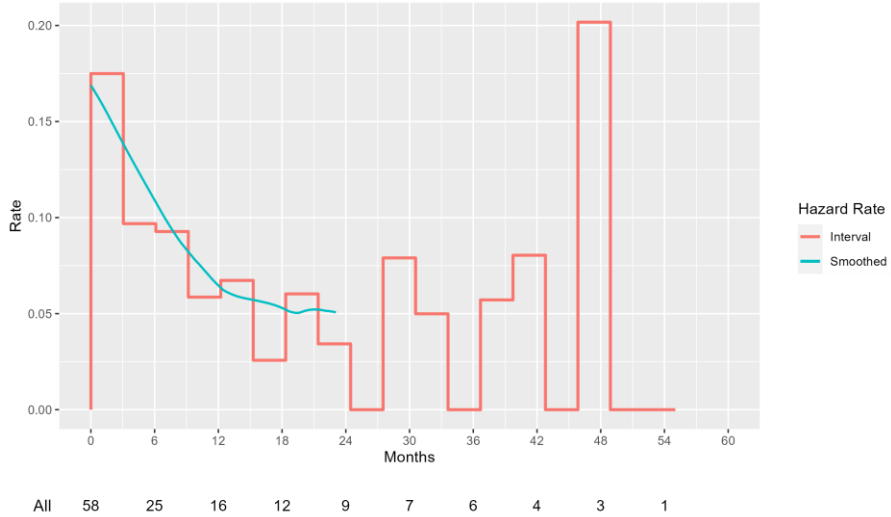


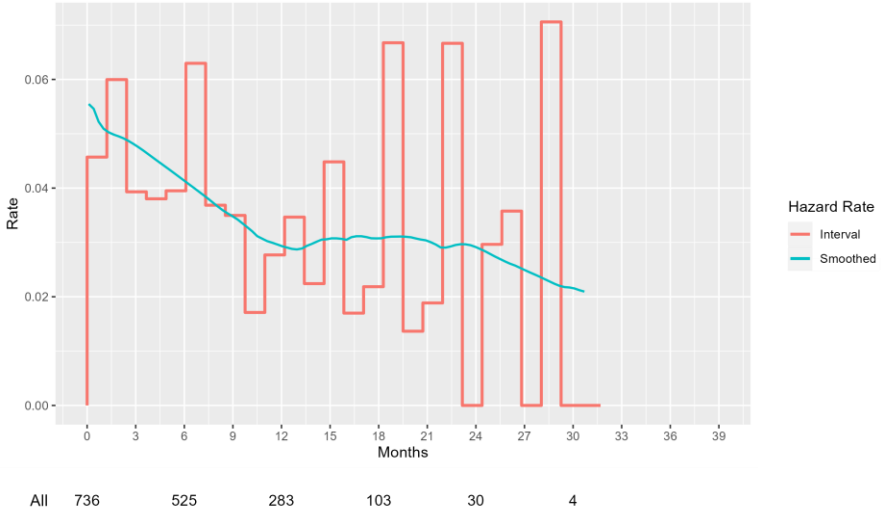
Figure 17. IsaPd TTD, ICARIA-MM

[redacted]

Figure 18. Pd TTD, ICARIA-MM

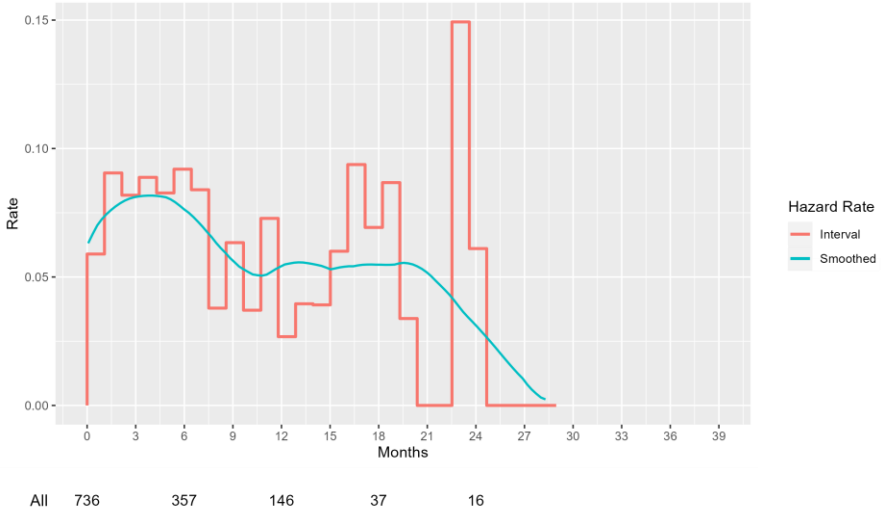
[redacted]

Figure 19. IsaPd OS, SACT



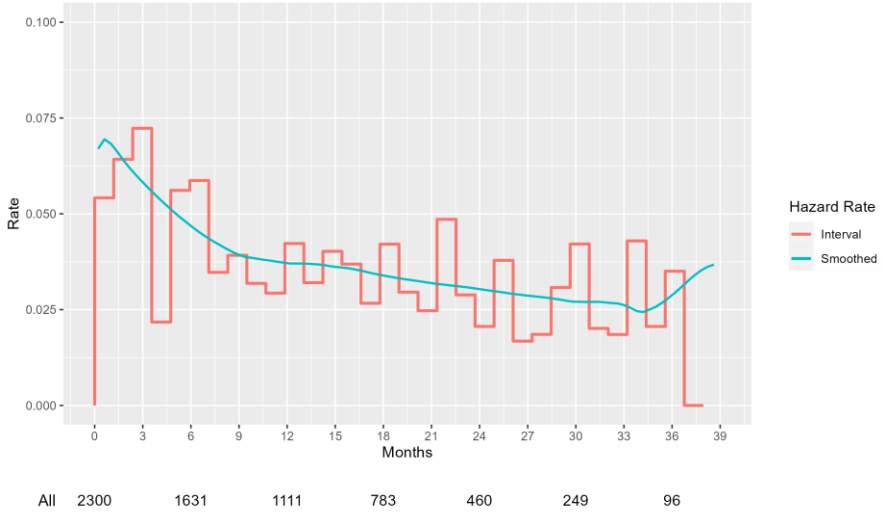
All	736	525	283	103	30	4

Figure 20. IsaPd TTD, SACT



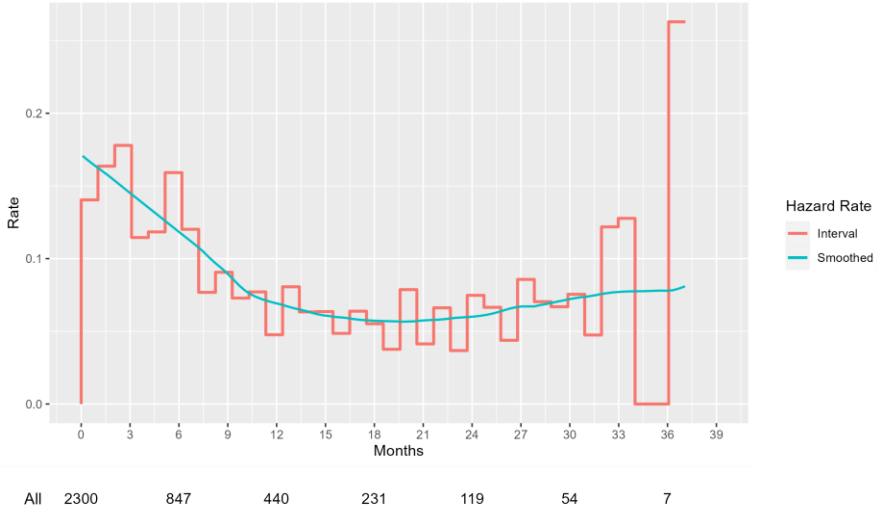
All	736	357	146	37	16	

Figure 21. Daratumumab OS, SACT



All	2300	1631	1111	783	460	249	96

Figure 22. Daratumumab TTD, SACT



All	2300	847	440	231	119	54	7

B12. Priority. IsaPd and Pd survival extrapolation:

a. Appendix S: values in Table 107 and Table 109 are identical. Please provide the correct values. Please also add the assessment for fitting a gamma distribution and the spline models with two and three knots.

Updated OS independent model goodness of fit statistics are presented in The choice of survival distribution in the company base case was carefully considered and approached in a systematic way. More mature OS data from ICARIA-MM were now available (52.4 months median follow-up, 38.5% of patients in the IsaPd arm and 27.6% of patients in the Pd arm remained censored for an OS event), and with survival probability available for 3 and 5 years. The Schoenfeld test when applied to this longer term data, indicated that the proportional hazards assumption for OS was not violated. Therefore, jointly fitted curves were considered appropriate. Amongst the jointly fitted distributions, the lognormal distribution most closely replicated the trial probabilities for both IsaPd and Pd at 3 years and 5 years and suggested survival probabilities beyond the trial that were clinically plausible. Jointly fitted exponential distributions (distribution preferred by the clinical experts) resulted in under prediction of patients alive at 5 years in both IsaPd and Pd in comparison to the trial data and therefore may have unduly penalised the longer term estimation.

Despite there being no suggestion of proportionality being violated within the final data cut from ICARIA-MM, independently fitted curves were also considered from the perspective of fit statistics, visual fit to the trial data and clinical plausibility beyond the trial. In the case of IsaPd, the exponential was considered to have best statistical fit however this also underestimated the proportion of patients alive compared to the trial for 3 and 5 years. For Pd, the best statistical fit was the lognormal distribution, however this resulted in higher probability of patients being alive at 3 and 5 years, timepoints for which data are available from ICARIA-MM.

Therefore having considered the above factors, jointly fitted curves were considered most appropriate for this comparison.

Table 34 and Table 35 for IsaPd and Pd, respectively with the inclusion of the gamma distribution and two and three knot spline models.

The choice of survival distribution in the company base case was carefully considered and approached in a systematic way. More mature OS data from ICARIA-MM were now available (52.4 months median follow-up, 38.5% of patients in the IsaPd arm and 27.6% of patients in the Pd arm remained censored for an OS event), and with survival probability available for 3 and 5 years. The Schoenfeld test when applied to this longer term data, indicated that the proportional hazards assumption for OS was not violated. Therefore, jointly fitted curves were considered appropriate. Amongst the jointly fitted distributions, the lognormal distribution most closely replicated the trial probabilities for both IsaPd and Pd at 3 years and 5 years and suggested survival probabilities beyond the trial that were clinically plausible. Jointly fitted exponential distributions (distribution preferred by the clinical experts) resulted in under prediction of patients alive at 5 years in both IsaPd and Pd in comparison to the trial data and therefore may have unduly penalised the longer term estimation.

Despite there being no suggestion of proportionality being violated within the final data cut from ICARIA-MM, independently fitted curves were also considered from the perspective of fit statistics, visual fit to the trial data and clinical plausibility beyond the trial. In the case of IsaPd, the exponential was considered to have best statistical fit however this also underestimated the proportion of patients alive compared to the trial for 3 and 5 years. For Pd, the best statistical fit was the lognormal distribution, however this resulted in higher probability of patients being alive at 3 and 5 years, timepoints for which data are available from ICARIA-MM.

Therefore having considered the above factors, jointly fitted curves were considered most appropriate for this comparison.

Table 34: IsaPd OS independent model statistical goodness of fit [update to Table 107 in CS]

Distribution	AIC	AICc	BIC
Exponential	313.3	313.4	315.3
Lognormal	312.0	312.2	315.9
Log-Logistic	313.5	313.7	317.4
Gamma	314.8	315.0	318.7
Weibull	315.0	315.3	318.9
Gompertz	315.3	315.6	319.2
Gen. Gamma	313.4	313.9	319.3
RCS Lognormal (one knot)	313.8	314.3	319.6
RCS Weibull (one knot)	314.8	315.3	320.6
RCS Log-Logistic (one knot)	314.8	315.3	320.7
RCS Lognormal 2k	315.1	315.9	322.9
Gen. F	315.4	316.3	323.2
RCS Log-Logistic 2k	315.9	316.7	323.7
RCS Lognormal 3k	314.1	315.4	323.8
RCS Weibull 2k	316.1	317.0	323.9
RCS Log-Logistic 3k	314.4	315.7	324.1
RCS Weibull 3k	314.9	316.2	324.7

Abbreviations: AIC, Akaike's Information Criterion; AICc, Akaike's Information Criterion Corrected; BIC, Bayesian Information Criterion; DF, degrees of freedom; IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; RCS, restricted cubic splines.

Table 35: Pd OS independent model statistical goodness of fit [update to Table 109 in CS]

Distribution	AIC	AICc	BIC
Lognormal	375.9	376.1	380.0
Log-Logistic	376.4	376.6	380.5
Gompertz	376.6	376.9	380.8
Exponential	379.3	379.3	381.3
Gen. Gamma	377.8	378.3	384.0

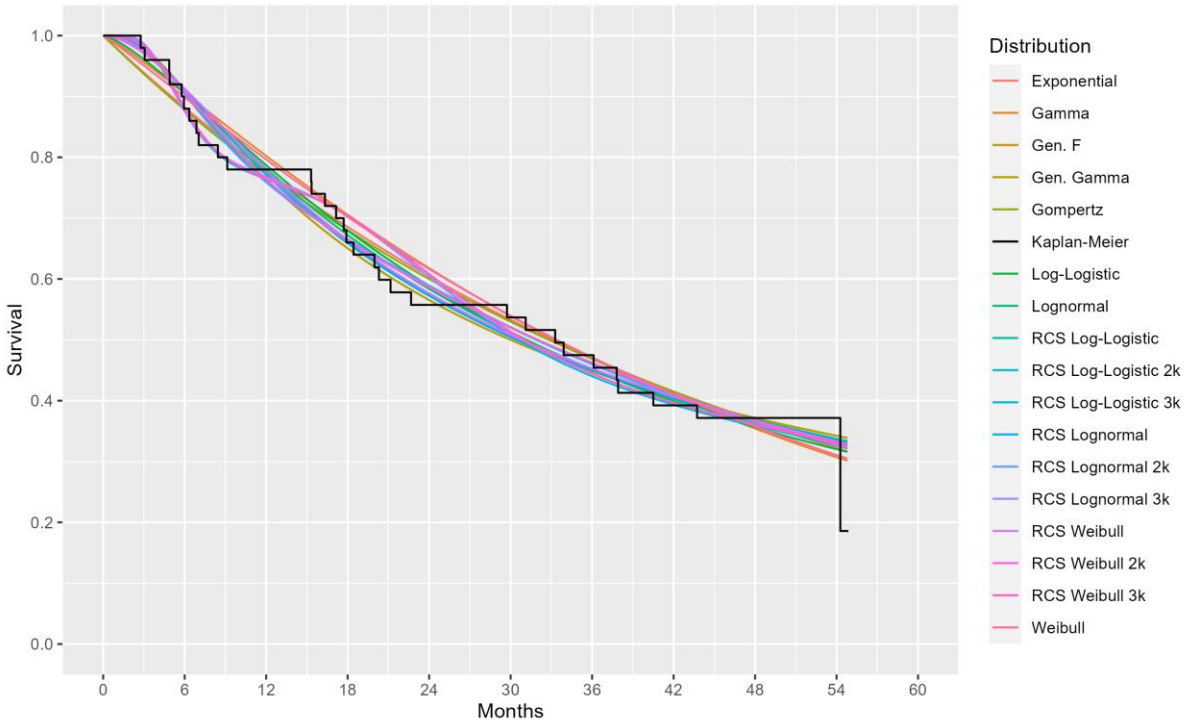
Distribution	AIC	AICc	BIC
RCS Log-Logistic	377.8	378.2	384.0
RCS Lognormal	377.9	378.3	384.0
Weibull	380.0	380.2	384.1
RCS Weibull	378.5	378.9	384.7
Gamma	380.6	380.8	384.8
RCS Log-Logistic 2k	379.4	380.2	387.7
Gen. F	379.6	380.3	387.8
RCS Lognormal 2k	379.9	380.6	388.1
RCS Weibull 2k	380.3	381.0	388.5
RCS Log-Logistic 3k	381.5	382.6	391.8
RCS Lognormal 3k	381.8	383.0	392.1
RCS Weibull 3k	381.9	383.1	392.3

Abbreviations: AIC, Akaike's Information Criterion; AICc, Akaike's Information Criterion Corrected; BIC, Bayesian Information Criterion; IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; RCS, restricted cubic splines.

b. For each time-to-event outcome which requires extrapolation, please provide the fitted models for the IsaPd arm (using the standard parametric distributions including exponential, Weibull, Gompertz, log-logistic, lognormal, gamma and generalised gamma based on the independent fitting approach) overlaying the KM curve to allow for visual assessment of the fit in a single plot. Please repeat this for the Pd arm. Please also provide the predicted survival probabilities at 3, 5, 10, 15 and 30 years based on the fitted models using the independent fitting approach in a table.

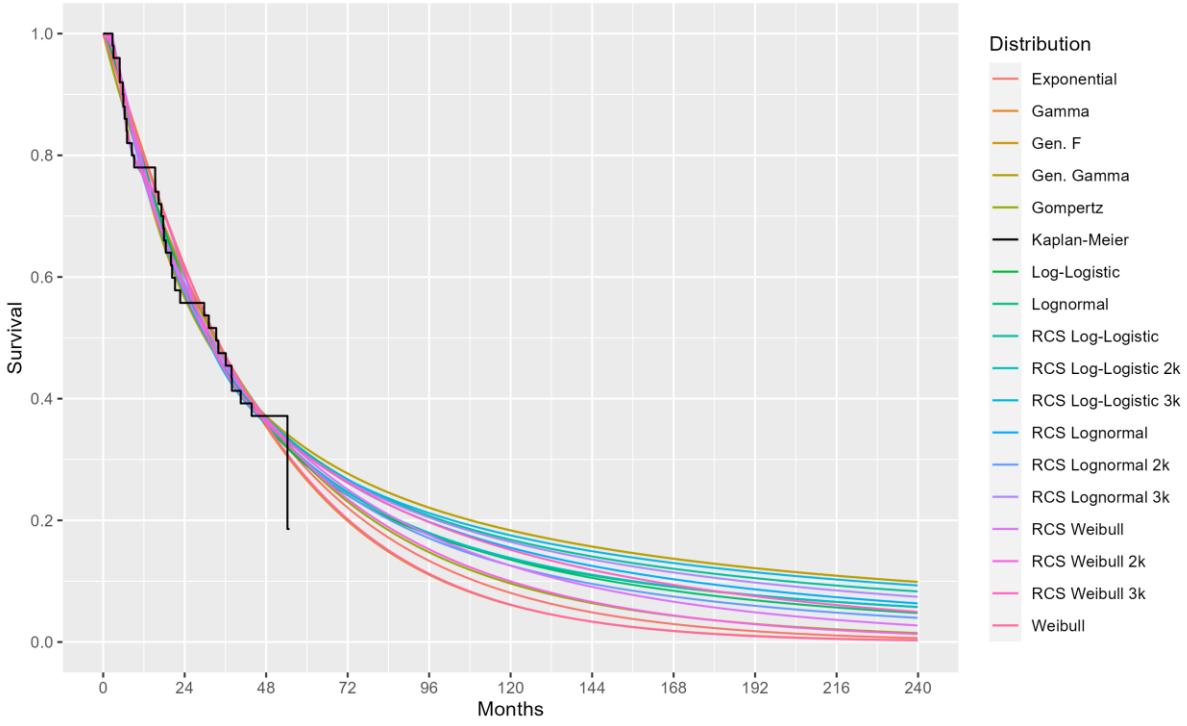
Independently fitted models to time to event outcomes for the IsaPd and Pd arms have been presented below. The predicted survival probabilities at specified time points have also been provided. Please note, the presented extrapolated curves and survival probabilities at specified time points exclude the application of general population mortality and the adjustment such that the PFS curve does not exceed OS, which are applied in the cost-effectiveness model.

Figure 23. IsaPd OS, ICARIA-MM, independently fitted



Abbreviations: 2k, two knots; 3k, three knots; IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; RCS, restricted cubic spline.

Figure 24. IsaPd OS, ICARIA-MM independently fitted to 20 year time horizon



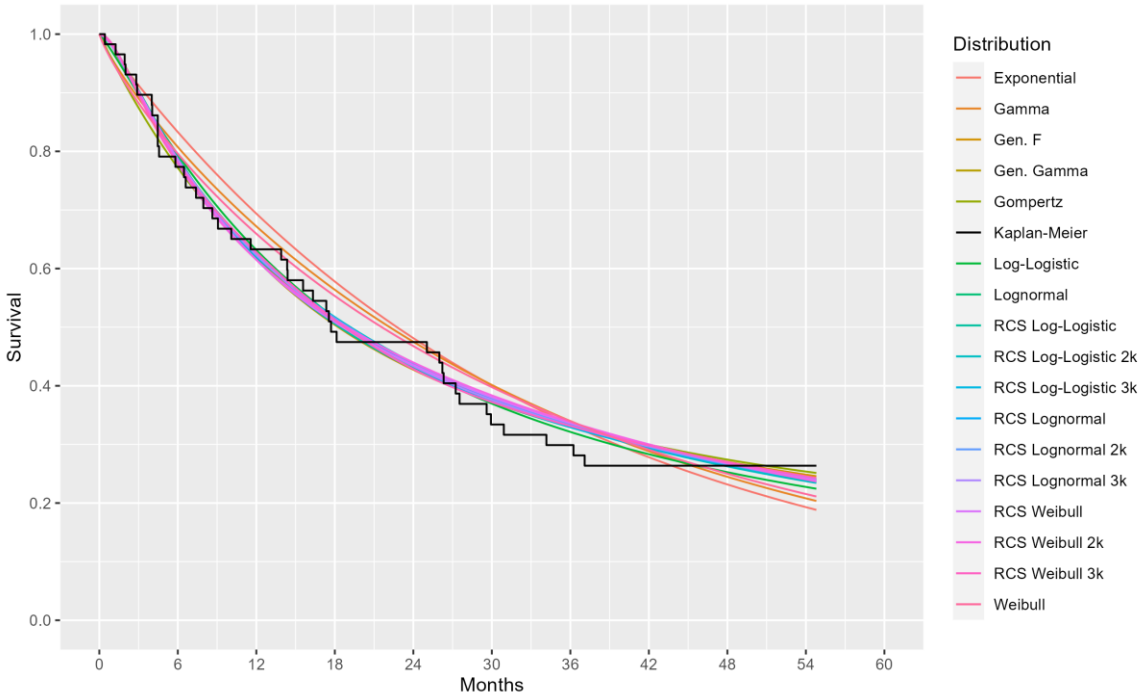
Abbreviations: 2k, two knots; 3k, three knots; IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; RCS, restricted cubic spline.

Table 36. IsaPd OS, ICARIA-MM Predicted survival probabilities at 3, 5, 10, 15 and 30 years

	Year				
Distribution	**3**	**5**	**10**	**15**	**30**
Exponential	0.4700	0.2841	0.0807	0.0229	0.0005
Gamma	0.4695	0.2659	0.0610	0.0136	0.0001
Gen. F	0.4482	0.3174	0.1836	0.1288	0.0671
Gen. Gamma	0.4482	0.3173	0.1835	0.1286	0.0670
Gompertz	0.4686	0.2906	0.0962	0.0358	0.0033
Log-Logistic	0.4509	0.2897	0.1363	0.0830	0.0339
Lognormal	0.4524	0.2958	0.1352	0.0759	0.0228
RCS Log-Logistic	0.4498	0.3108	0.1681	0.1122	0.0536
RCS Log-Logistic 2k	0.4598	0.2961	0.1382	0.0836	0.0336
RCS Log-Logistic 3k	0.4402	0.3061	0.1753	0.1218	0.0627
RCS Lognormal	0.4501	0.3073	0.1550	0.0944	0.0339
RCS Lognormal 2k	0.4611	0.2945	0.1257	0.0666	0.0175
RCS Lognormal 3k	0.4444	0.3059	0.1645	0.1056	0.0428
RCS Weibull	0.4529	0.3024	0.1254	0.0569	0.0069
RCS Weibull 2k	0.4624	0.2931	0.0998	0.0357	0.0019
RCS Weibull 3k	0.4445	0.3057	0.1515	0.0840	0.0194
Weibull	0.4714	0.2695	0.0616	0.0131	0.0001

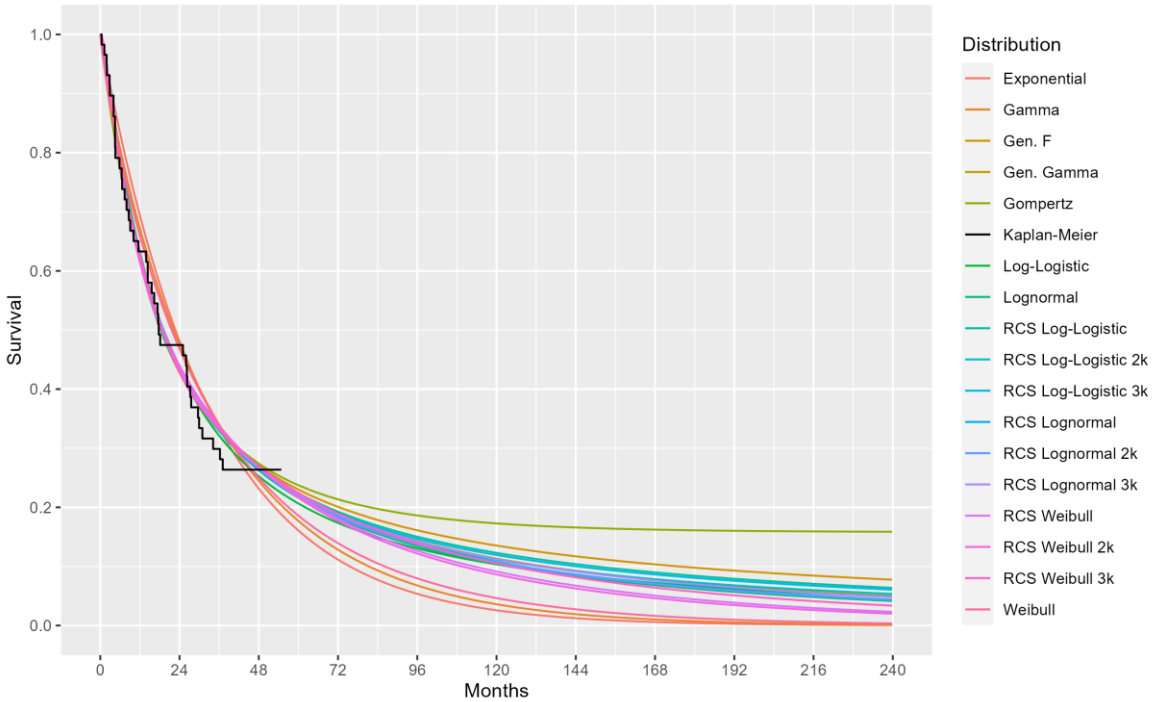
Abbreviations: 2k, two knots; 3k, three knots; IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; RCS, restricted cubic spline.

Figure 25. Pd OS, ICARIA-MM, independently fitted



Abbreviations: 2k, two knots; 3k, three knots; OS, overall survival; Pd, pomalidomide + dexamethasone; RCS, restricted cubic splines.

Figure 26. Pd OS, ICARIA-MM, independently fitted to 20 year time horizon



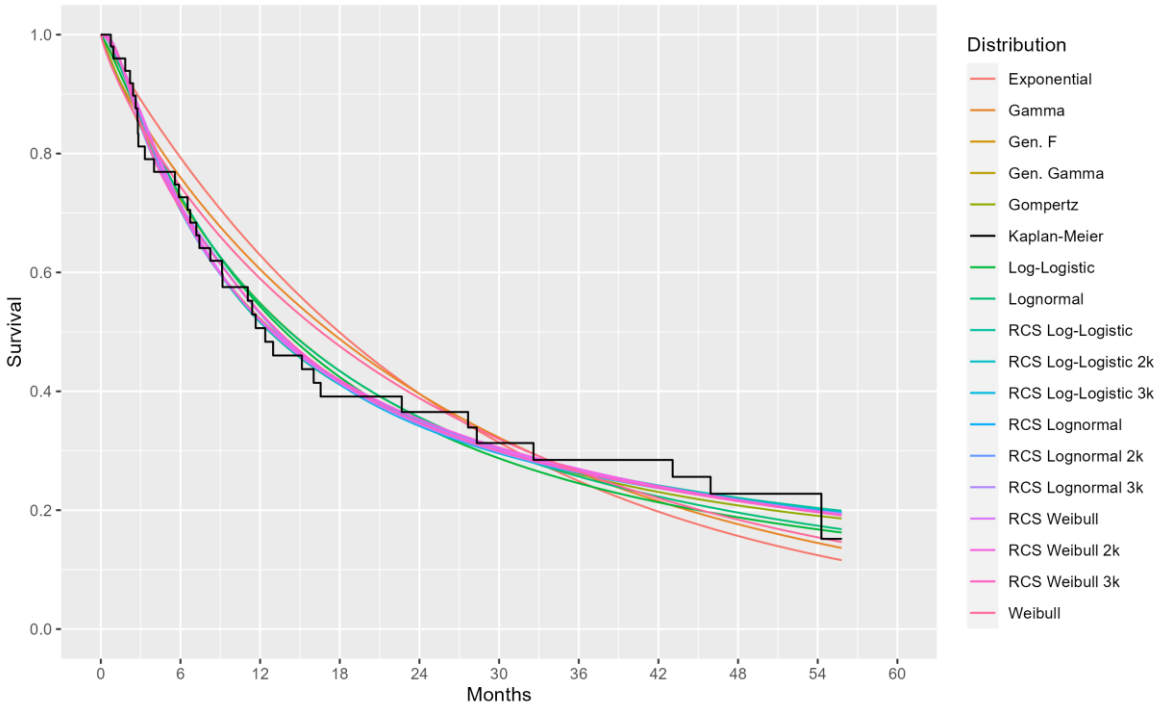
Abbreviations: 2k, two knots; 3k, three knots; OS, overall survival; Pd, pomalidomide + dexamethasone; RCS, restricted cubic splines.

Table 37: Pd OS, ICARIA-MM Predicted survival probabilities at 3, 5, 10, 15 and 30 years

	Year				
Distribution	**3**	**5**	**10**	**15**	**30**
Exponential	0.3340	0.1608	0.0258	0.0042	0.0000
Gamma	0.3400	0.1769	0.0360	0.0075	0.0001
Gen. F	0.3300	0.2300	0.1353	0.0979	0.0556
Gen. Gamma	0.3336	0.2225	0.1133	0.0714	0.0290
Gompertz	0.3329	0.2374	0.1728	0.1611	0.1580
Log-Logistic	0.3214	0.2065	0.1035	0.0670	0.0309
Lognormal	0.3323	0.2166	0.1040	0.0621	0.0221
RCS Log-Logistic	0.3293	0.2239	0.1230	0.0842	0.0428
RCS Log-Logistic 2k	0.3308	0.2162	0.1111	0.0729	0.0344
RCS Log-Logistic 3k	0.3294	0.2214	0.1193	0.0807	0.0402
RCS Lognormal	0.3332	0.2193	0.1074	0.0651	0.0239
RCS Lognormal 2k	0.3336	0.2188	0.1064	0.0642	0.0233
RCS Lognormal 3k	0.3318	0.2220	0.1124	0.0699	0.0271
RCS Weibull	0.3364	0.2184	0.0913	0.0442	0.0074
RCS Weibull 2k	0.3382	0.2162	0.0865	0.0400	0.0058
RCS Weibull 3k	0.3315	0.2245	0.1053	0.0572	0.0134
Weibull	0.3396	0.1859	0.0464	0.0127	0.0003

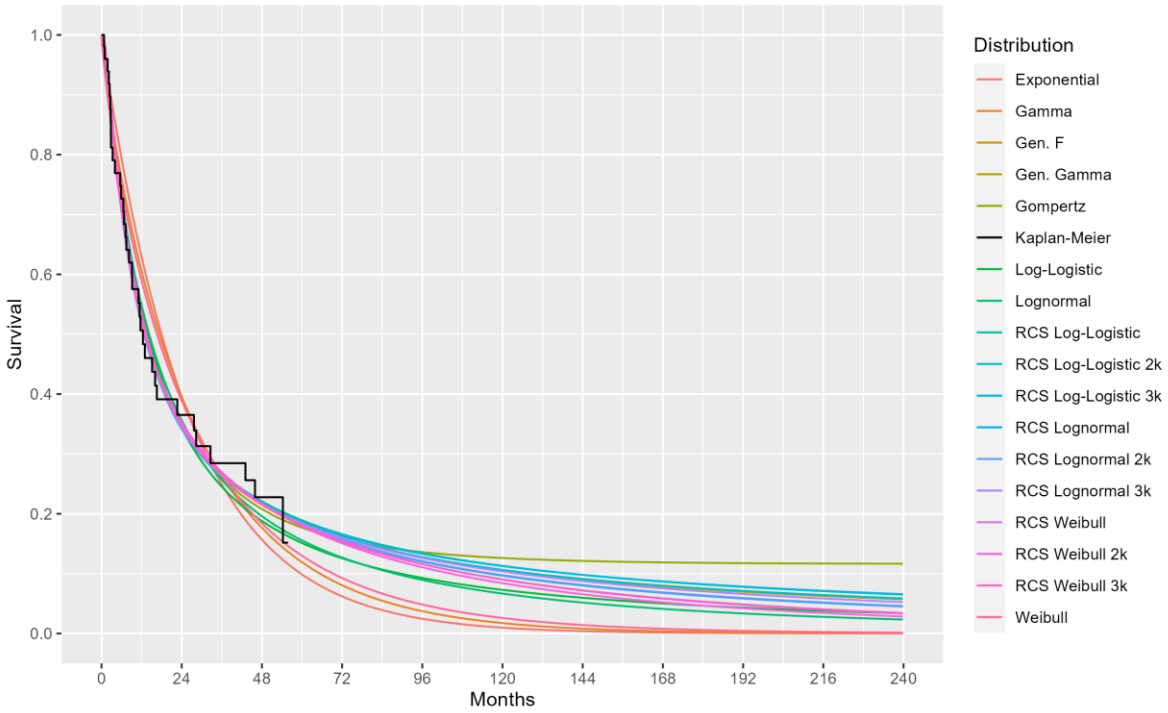
Abbreviations: 2k, two knots; 3k, three knots; OS, overall survival; Pd, pomalidomide + dexamethasone; RCS, restricted cubic splines.

Figure 27. IsaPd PFS, ICARIA-MM, independently fitted



Abbreviations: 2k, two knots; 3k, three knots; IsaPd, isatuximab + pomalidomide + dexamethasone; PFS, progression-free survival; RCS, restricted cubic splines.

Figure 28. IsaPd PFS, ICARIA-MM, independently fitted to 20 year time horizon



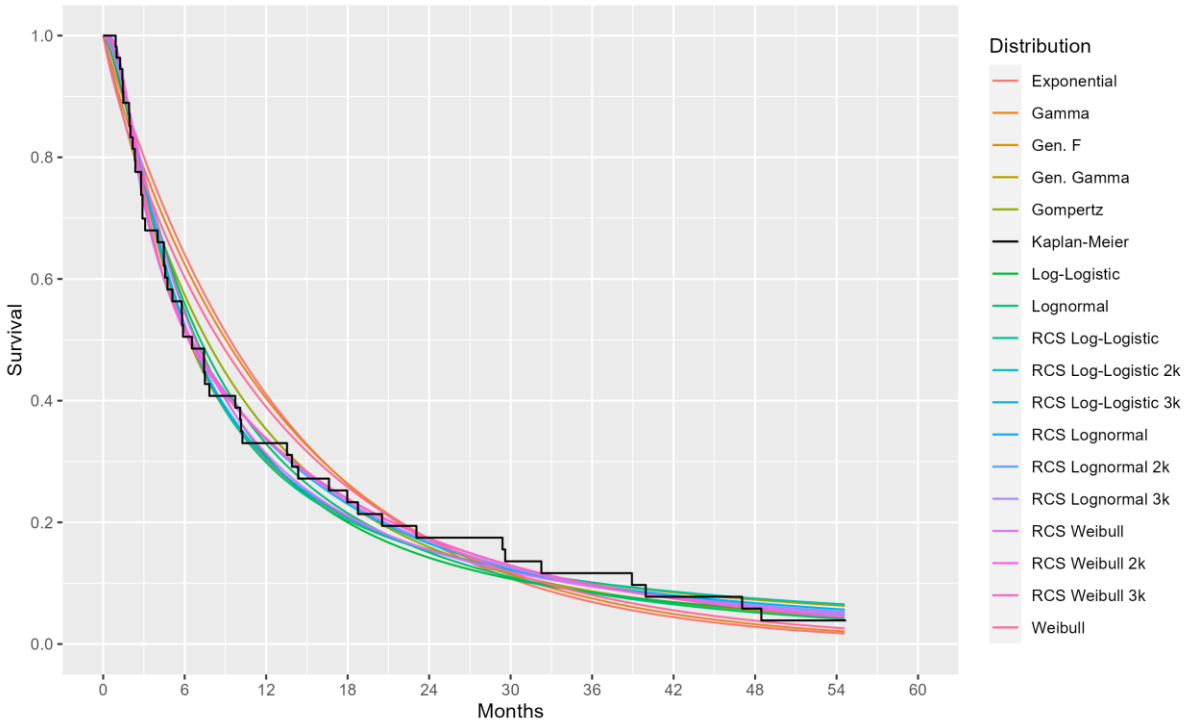
Abbreviations: 2k, two knots; 3k, three knots; IsaPd, isatuximab + pomalidomide + dexamethasone; PFS, progression-free survival; RCS, restricted cubic splines.

Table 38. IsaPd PFS, ICARIA-MM Predicted survival probabilities at 3, 5, 10, 15 and 30 years

Distribution	Year				
	3	5	10	15	30
Exponential	0.2490	0.0986	0.0097	0.0010	0.0000
Gamma	0.2631	0.1190	0.0173	0.0026	0.0000
Gen. F	0.2680	0.1841	0.1051	0.0740	0.0394
Gen. Gamma	0.2680	0.1841	0.1050	0.0739	0.0393
Gompertz	0.2605	0.1768	0.1261	0.1180	0.1162
Log-Logistic	0.2453	0.1511	0.0729	0.0465	0.0211
Lognormal	0.2567	0.1555	0.0667	0.0370	0.0115
RCS Log-Logistic	0.2676	0.1891	0.1129	0.0820	0.0464
RCS Log-Logistic 2k	0.2686	0.1853	0.1063	0.0753	0.0408
RCS Log-Logistic 3k	0.2623	0.1863	0.1126	0.0824	0.0474
RCS Lognormal	0.2687	0.1820	0.0966	0.0629	0.0272
RCS Lognormal 2k	0.2686	0.1825	0.0975	0.0637	0.0278
RCS Lognormal 3k	0.2637	0.1839	0.1036	0.0704	0.0334
RCS Weibull	0.2673	0.1816	0.0901	0.0527	0.0157
RCS Weibull 2k	0.2696	0.1792	0.0841	0.0467	0.0121
RCS Weibull 3k	0.2646	0.1801	0.0903	0.0533	0.0163
Weibull	0.2647	0.1298	0.0259	0.0059	0.0001

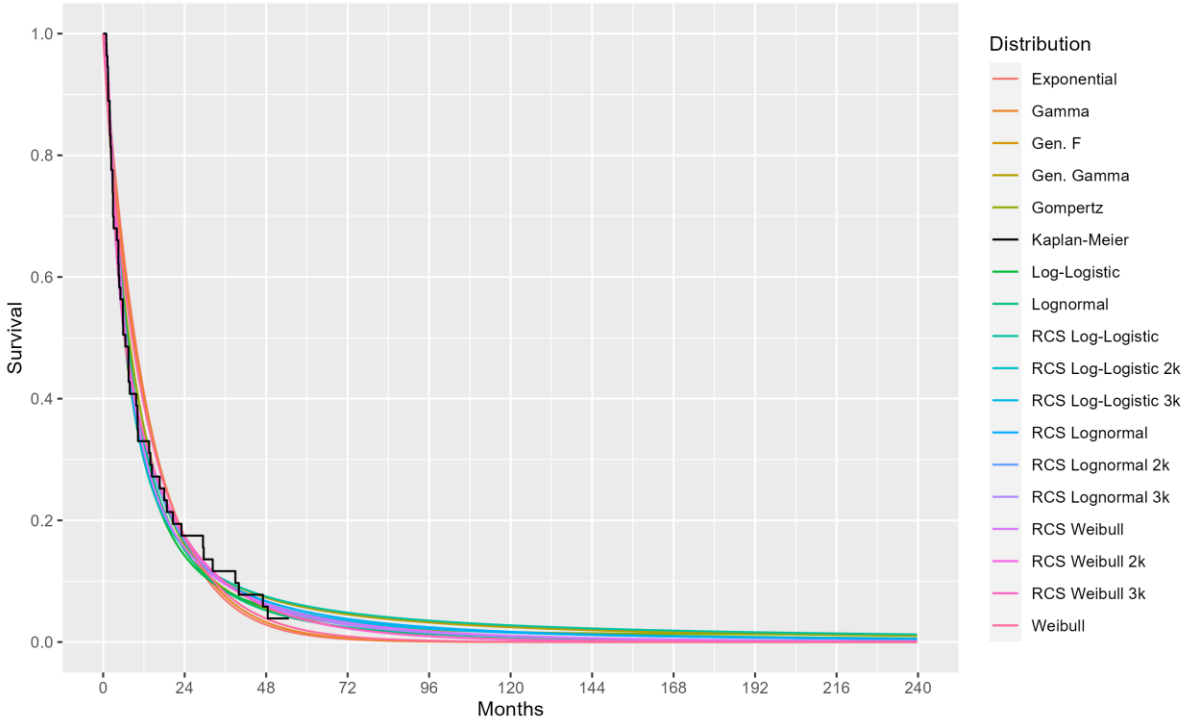
Abbreviations: 2k, two knots; 3k, three knots; IsaPd, isatuximab + pomalidomide + dexamethasone; PFS, progression-free survival; RCS, restricted cubic splines.

Figure 29. Pd PFS, ICARIA-MM, independently fitted



Abbreviations: 2k, two knots; 3k, three knots; Pd, pomalidomide + dexamethasone; PFS, progression-free survival; RCS, restricted cubic splines.

Figure 30. Pd PFS, ICARIA-MM, independently fitted to 20 year time horizon



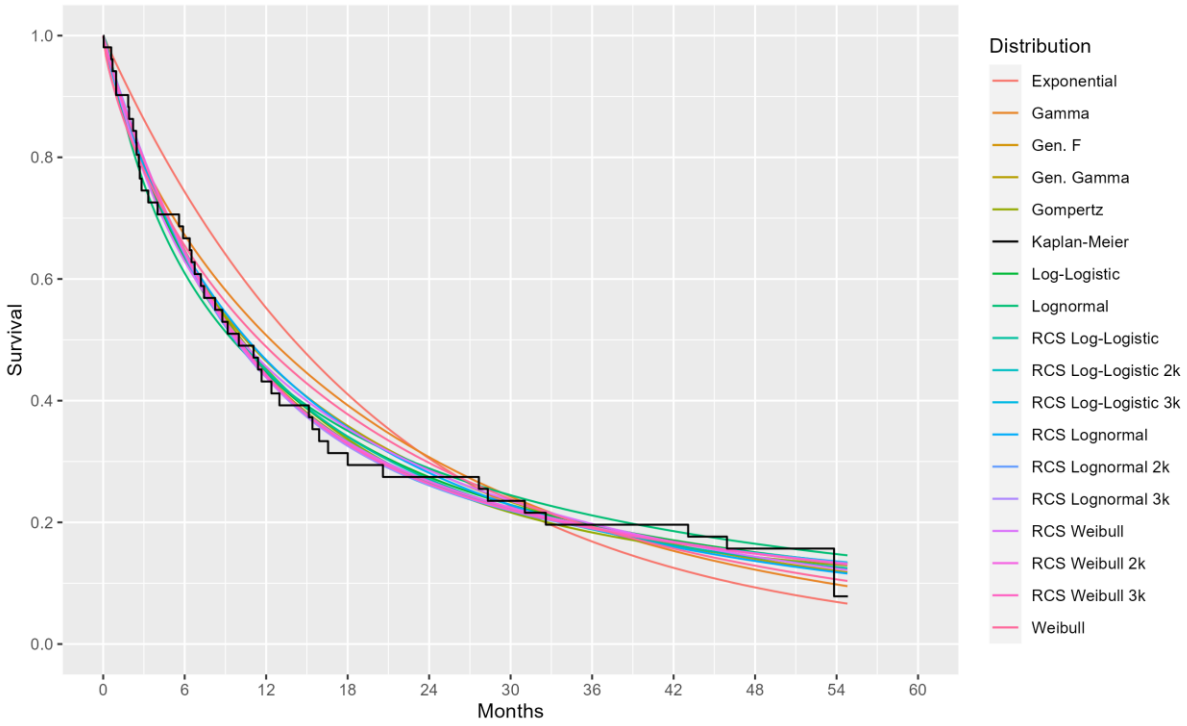
Abbreviations: 2k, two knots; 3k, three knots; Pd, pomalidomide + dexamethasone; PFS, progression-free survival; RCS, restricted cubic splines.

Table 39. Pd PFS, ICARIA-MM Predicted survival probabilities at 3, 5, 10, 15 and 30 years

Distribution	Year				
	3	5	10	15	30
Exponential	0.0690	0.0116	0.0001	0.0000	0.0000
Gamma	0.0749	0.0143	0.0002	0.0000	0.0000
Gen. F	0.1007	0.0564	0.0245	0.0148	0.0061
Gen. Gamma	0.1006	0.0563	0.0245	0.0148	0.0061
Gompertz	0.0867	0.0382	0.0163	0.0131	0.0121
Log-Logistic	0.0846	0.0425	0.0161	0.0091	0.0034
Lognormal	0.0836	0.0346	0.0080	0.0029	0.0004
RCS Log-Logistic	0.1013	0.0590	0.0275	0.0174	0.0079
RCS Log-Logistic 2k	0.0964	0.0457	0.0159	0.0085	0.0029
RCS Log-Logistic 3k	0.0962	0.0451	0.0154	0.0081	0.0027
RCS Lognormal	0.0970	0.0496	0.0169	0.0082	0.0020
RCS Lognormal 2k	0.0960	0.0406	0.0096	0.0036	0.0005
RCS Lognormal 3k	0.0960	0.0401	0.0093	0.0034	0.0005
RCS Weibull	0.0944	0.0441	0.0106	0.0034	0.0003
RCS Weibull 2k	0.0978	0.0354	0.0043	0.0007	0.0000
RCS Weibull 3k	0.0976	0.0357	0.0044	0.0007	0.0000
Weibull	0.0805	0.0187	0.0006	0.0000	0.0000

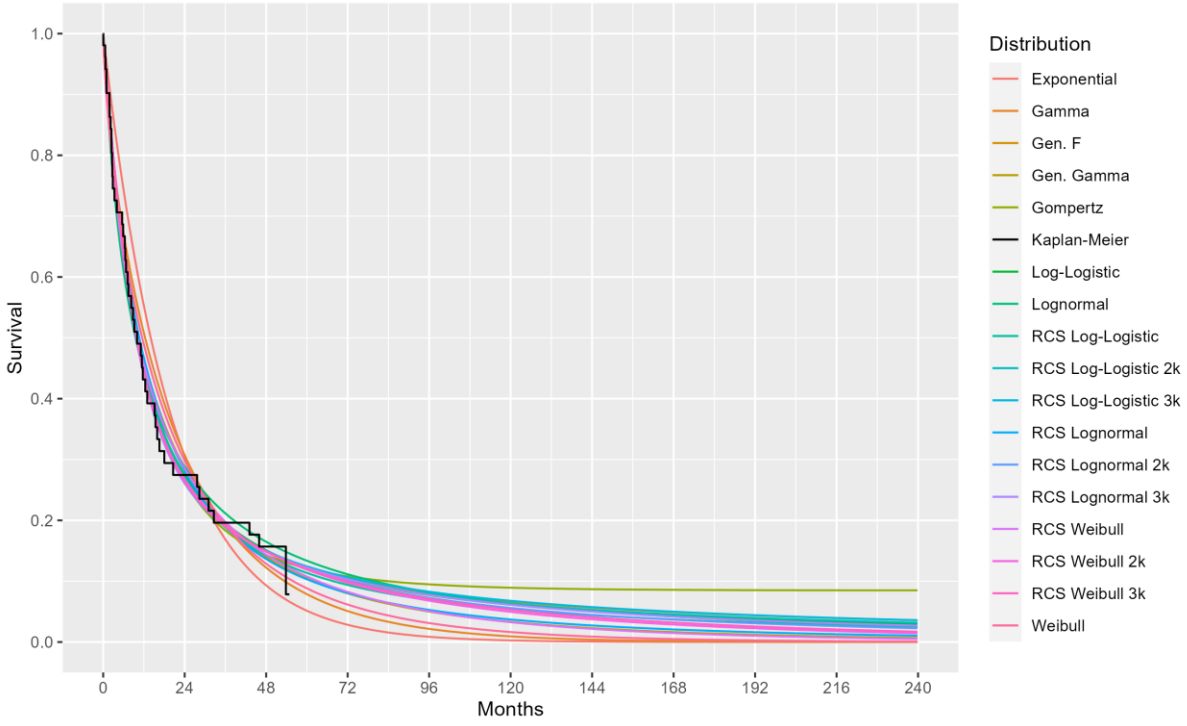
Abbreviations: 2k, two knots; 3k, three knots; Pd, pomalidomide + dexamethasone; PFS, progression-free survival; RCS, restricted cubic splines.

Figure 31. IsaPd PFS On-Tx, ICARIA-MM, independently fitted



Abbreviations: 2k, two knots; 3k, three knots; IsaPd, isatuximab + pomalidomide + dexamethasone; PFS On-Tx, progression-free survival on treatment; RCS, restricted cubic splines.

Figure 32. IsaPd PFS On-Tx, ICARIA-MM, independently fitted to 20 year time horizon



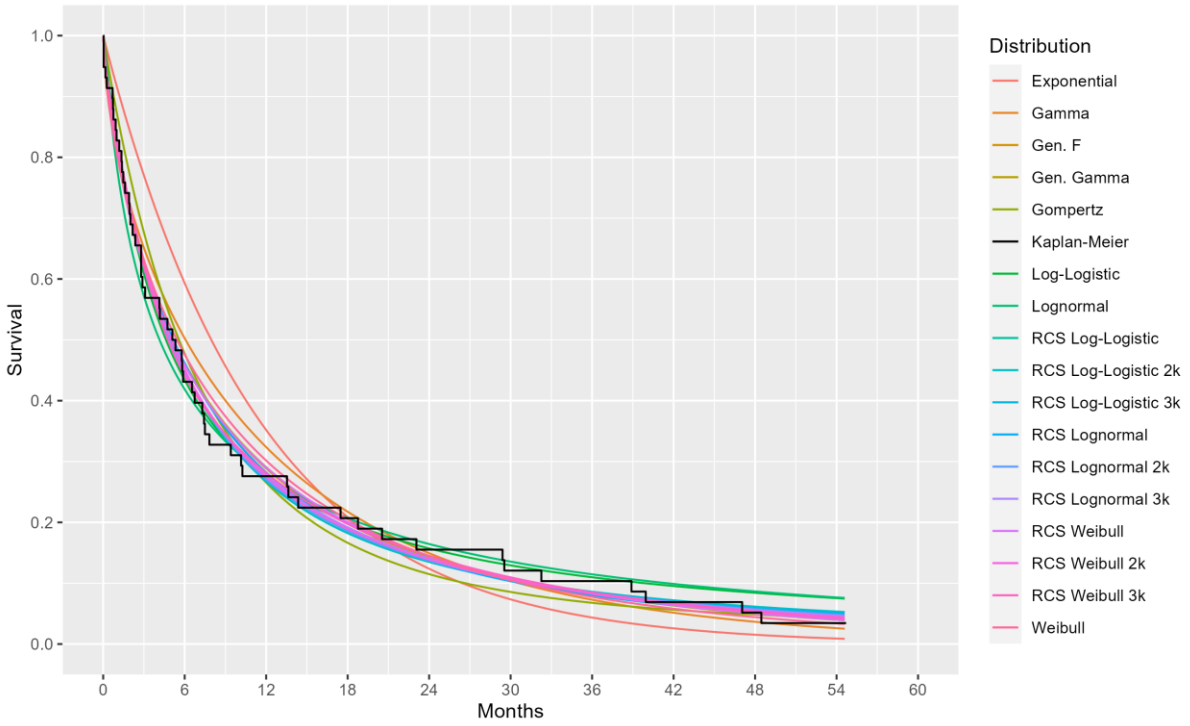
Abbreviations: 2k, two knots; 3k, three knots; IsaPd, isatuximab + pomalidomide + dexamethasone; PFS On-Tx, progression-free survival on treatment; RCS, restricted cubic splines.

Table 40. IsaPd PFS On-Tx, ICARIA-MM Predicted survival probabilities at 3, 5, 10, 15 and 30 years

Distribution	Year				
	3	5	10	15	30
Exponential	0.1685	0.0514	0.0026	0.0001	0.0000
Gamma	0.1922	0.0786	0.0093	0.0012	0.0000
Gen. F	0.1902	0.1224	0.0664	0.0463	0.0250
Gen. Gamma	0.1944	0.1043	0.0332	0.0139	0.0021
Gompertz	0.1834	0.1210	0.0893	0.0855	0.0849
Log-Logistic	0.1956	0.1223	0.0614	0.0404	0.0194
Lognormal	0.2114	0.1336	0.0634	0.0382	0.0143
RCS Log-Logistic	0.1884	0.1136	0.0541	0.0344	0.0156
RCS Log-Logistic 2k	0.1915	0.1220	0.0633	0.0424	0.0211
RCS Log-Logistic 3k	0.1893	0.1244	0.0678	0.0469	0.0246
RCS Lognormal	0.1894	0.1031	0.0371	0.0183	0.0045
RCS Lognormal 2k	0.1924	0.1200	0.0560	0.0336	0.0124
RCS Lognormal 3k	0.1896	0.1224	0.0611	0.0385	0.0157
RCS Weibull	0.1975	0.1077	0.0326	0.0123	0.0012
RCS Weibull 2k	0.1926	0.1190	0.0496	0.0254	0.0056
RCS Weibull 3k	0.1901	0.1201	0.0530	0.0286	0.0073
Weibull	0.1925	0.0883	0.0165	0.0038	0.0001

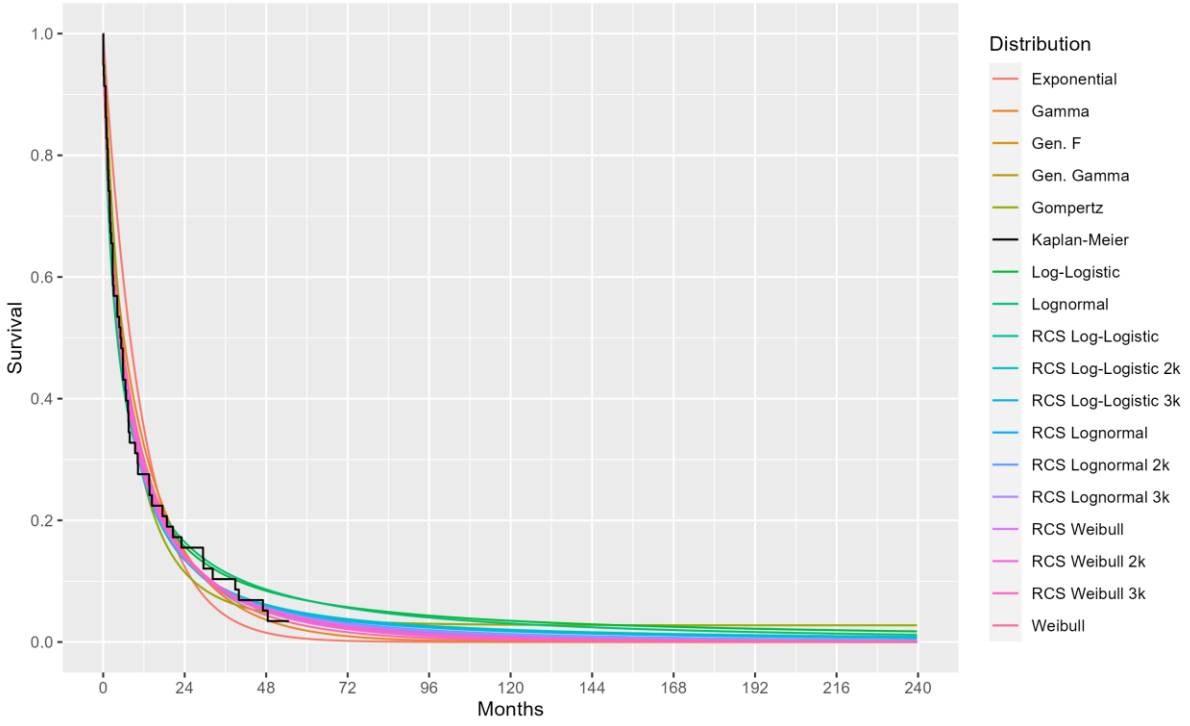
Abbreviations: 2k, two knots; 3k, three knots; IsaPd, isatuximab + pomalidomide + dexamethasone; PFS On-Tx, progression-free survival on treatment; RCS, restricted cubic splines.

Figure 33. Pd PFS On-Tx, ICARIA-MM, independently fitted



Abbreviations: 2k, two knots; 3k, three knots; Pd, pomalidomide + dexamethasone; PFS On-Tx, progression-free survival on treatment; RCS, restricted cubic splines.

Figure 34. Pd PFS On-Tx, ICARIA-MM, independently fitted to 20 year time horizon



Abbreviations: 2k, two knots; 3k, three knots; Pd, pomalidomide + dexamethasone; PFS On-Tx, progression-free survival on treatment; RCS, restricted cubic splines.

Table 41. Pd PFS On-Tx, ICARIA-MM Predicted survival probabilities at 3, 5, 10, 15 and 30 years

Distribution	Year				
	3	5	10	15	30
Exponential	0.0435	0.0054	0.0000	0.0000	0.0000
Gamma	0.0729	0.0186	0.0007	0.0000	0.0000
Gen. F	0.0814	0.0334	0.0067	0.0020	0.0002
Gen. Gamma	0.0814	0.0321	0.0054	0.0013	0.0001
Gompertz	0.0678	0.0394	0.0285	0.0276	0.0275
Log-Logistic	0.1098	0.0683	0.0349	0.0233	0.0116
Lognormal	0.1146	0.0686	0.0306	0.0180	0.0065
RCS Log-Logistic	0.0856	0.0467	0.0199	0.0120	0.0050
RCS Log-Logistic 2k	0.0860	0.0471	0.0202	0.0122	0.0051
RCS Log-Logistic 3k	0.0857	0.0443	0.0175	0.0101	0.0039
RCS Lognormal	0.0801	0.0359	0.0097	0.0040	0.0007
RCS Lognormal 2k	0.0843	0.0414	0.0132	0.0061	0.0014
RCS Lognormal 3k	0.0846	0.0396	0.0116	0.0050	0.0010
RCS Weibull	0.0825	0.0321	0.0049	0.0011	0.0000
RCS Weibull 2k	0.0835	0.0370	0.0079	0.0023	0.0001
RCS Weibull 3k	0.0848	0.0348	0.0061	0.0015	0.0000
Weibull	0.0775	0.0263	0.0028	0.0004	0.0000

Abbreviations: 2k, two knots; 3k, three knots; Pd, pomalidomide + dexamethasone; PFS On-Tx, progression-free survival on treatment; RCS, restricted cubic splines.

Figure 35. IsaPd TTD, ICARIA-MM, independently fitted

Abbreviations: 2k, two knots; 3k, three knots; IsaPd, isatuximab + pomalidomide + dexamethasone; RCS, restricted cubic splines; TTD, time to discontinuation.

Figure 36. IsaPd TTD, ICARIA-MM, independently fitted to 20 year time horizon

Abbreviations: 2k, two knots; 3k, three knots; IsaPd, isatuximab + pomalidomide + dexamethasone; RCS, restricted cubic splines; TTD, time to discontinuation.

Table 42. IsaPd TTD, ICARIA-MM Predicted survival probabilities at 3, 5, 10, 15 and 30 years

Distribution	Year				
	3	5	10	15	30
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen. F	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen. Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Log-Logistic 2k	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Log-Logistic 3k	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Lognormal 2k	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Lognormal 3k	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Weibull 2k	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Weibull 3k	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2k, two knots; 3k, three knots; IsaPd, isatuximab + pomalidomide + dexamethasone; RCS, restricted cubic splines; TTD, time to discontinuation.

Figure 37. Pd TTD, ICARIA-MM, independently fitted

Abbreviations: 2k, two knots; 3k, three knots; Pd, pomalidomide + dexamethasone; RCS, restricted cubic splines; TTD, time to discontinuation.

Figure 38. Pd TTD, ICARIA-MM, independently fitted to 20 year time horizon

Abbreviations: 2k, two knots; 3k, three knots; Pd, pomalidomide + dexamethasone; RCS, restricted cubic splines; TTD, time to discontinuation.

Table 43. Pd TTD, ICARIA-MM Predicted survival probabilities at 3, 5, 10, 15 and 30 years

Distribution	Year				
	3	5	10	15	30
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen. F	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen. Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Log-Logistic 2k	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Log-Logistic 3k	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Lognormal 2k	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Lognormal 3k	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Weibull 2k	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Weibull 3k	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2k, two knots; 3k, three knots; Pd, pomalidomide + dexamethasone; RCS, restricted cubic splines; TTD, time to discontinuation.

c. Repeat (b) based on the restricted cubic spline (RCS) models with one, two, and three knots.

Included above in response to B12(b)

d. Please clarify how the IPCW and simple TSE adjusted HR were applied in the scenario analysis.

As part of the scenario analyses, IPCW and TSE analysis were both used to account for differences in the proportions of patients receiving daratumumab as subsequent therapy between the ICARIA-MM IsaPd and Pd arms and the effect of this difference on long-term survival. Both methods return an adjusted OS HR for IsaPd vs Pd.

The implementation of both these approaches in the model involved setting the base OS curve to what was used for the Pd comparator (in this case, OS: Pd Lognormal (R)), and then applying the respective adjusted hazard ratio.

B13. Priority. IsaPd and daratumumab monotherapy survival extrapolation:

a. Please provide both AIC and BIC scores for each arm based on the independent fitting approach in a table. Please also add the assessment for fitting a gamma distribution and the spline models with two and three knots.

Table 44 and Table 45 present the OS independent goodness of fit statistics for the IsaPd and daratumumab monotherapy arms respectively with the inclusion of the gamma models and spline models with two and three knots. The fit statistics for OS in the IsaPd SACT arm provide support to the company's choice for the base case curve- independently fitted lognormal. As noted in the CS, the Weibull fit to daratumumab SACT OS is not among the best fitting distributions but were chosen as it was accepted by the EAG and committee for TA783 (40) based on the same underlying data.

Table 44: IsaPd OS independent model statistical goodness of fit

Distribution	AIC	AICc	BIC
Lognormal	2,591.5	2,591.5	2,600.7
Log-Logistic	2,597.8	2,597.8	2,607.0
Gen. Gamma	2,593.5	2,593.5	2,607.3
RCS Lognormal	2,593.5	2,593.5	2,607.3
Gompertz	2,599.3	2,599.3	2,608.5
RCS Weibull	2,594.8	2,594.9	2,608.6
RCS Log-Logistic	2,596.1	2,596.2	2,609.9
Exponential	2,606.9	2,606.9	2,611.5
RCS Lognormal 2k	2,594.2	2,594.3	2,612.6
RCS Weibull 2k	2,595.1	2,595.2	2,613.5
RCS Log-Logistic 2k	2,595.3	2,595.4	2,613.7
Gen. F	2,595.5	2,595.6	2,613.9
Weibull	2,604.9	2,604.9	2,614.1
Gamma	2,606.2	2,606.2	2,615.4
RCS Weibull 3k	2,594.1	2,594.2	2,617.1
RCS Log-Logistic 3k	2,594.6	2,594.7	2,617.6
RCS Lognormal 3k	2,594.6	2,594.7	2,617.6

Abbreviations: 2k, 2 knot; 3k, 3 knot; AIC, Akaike's Information Criterion; AICc, Akaike's Information Criterion Corrected; BIC, Bayesian Information Criterion; DF, degrees of freedom; IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; RCS, restricted cubic splines.

Table 45: Daratumumab monotherapy OS independent model statistical goodness of fit

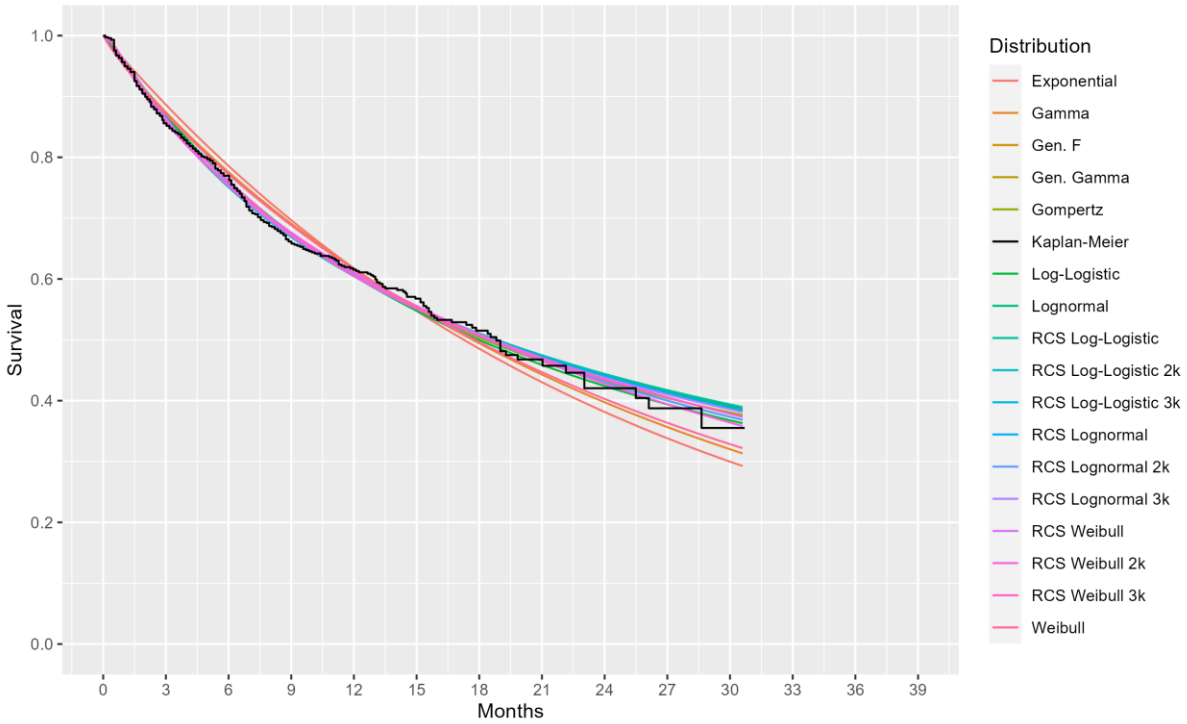
Distribution	AIC	AICc	BIC
RCS Lognormal 2k	11,241.3	11,241.3	11,264.3
RCS Lognormal 3k	11,239.3	11,239.4	11,268.0
Lognormal	11,264.7	11,264.7	11,276.2
RCS Log-Logistic 2k	11,257.2	11,257.2	11,280.1
RCS Log-Logistic 3k	11,251.9	11,251.9	11,280.6
RCS Weibull 3k	11,253.6	11,253.6	11,282.3
Gen. Gamma	11,265.9	11,265.9	11,283.2
RCS Lognormal	11,266.7	11,266.7	11,283.9
RCS Weibull 2k	11,262.8	11,262.8	11,285.7

Distribution	AIC	AICc	BIC
Gen. F	11,268.1	11,268.1	11,291.0
RCS Weibull	11,289.1	11,289.1	11,306.4
RCS Log-Logistic	11,298.1	11,298.1	11,315.3
Log-Logistic	11,305.5	11,305.5	11,316.9
Gompertz	11,316.3	11,316.3	11,327.8
Weibull	11,348.0	11,348.1	11,359.5
Gamma	11,361.0	11,361.0	11,372.5
Exponential	11,390.2	11,390.2	11,395.9

Abbreviations: 2k, 2 knot; 3k, 3 knot; AIC, Akaike's Information Criterion; AICc, Akaike's Information Criterion Corrected; BIC, Bayesian Information Criterion; DF, degrees of freedom; OS, overall survival; RCS, restricted cubic splines

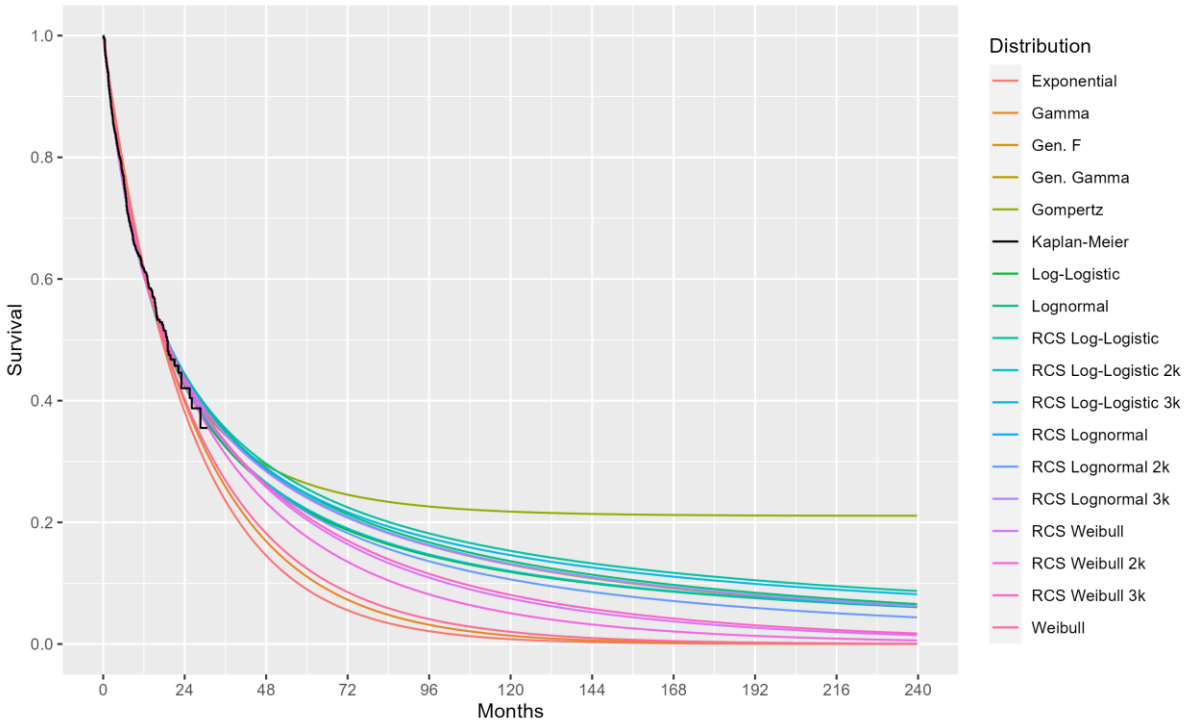
b. For each time-to-event outcome which requires extrapolation, please provide the fitted models for the IsaPd arm (using the standard parametric distributions including exponential, Weibull, Gompertz, log-logistic, lognormal, gamma and generalised gamma based on the independent fitting approach) overlaying the KM curve to allow for visual assessment of the fit in a single plot. Please repeat this for the daratumumab arm. Please also provide the predicted survival probabilities at 3, 5, 10, 15 and 30 years based on the fitted models using the independent fitting approach in a table.

Figure 39. IsaPd OS, SACT, independently fitted



Abbreviations: 2k, two knots; 3k, three knots; IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy.

Figure 40. IsaPd OS, SACT, independently fitted to 20 year time horizon



Abbreviations: 2k, two knots; 3k, three knots; IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy.

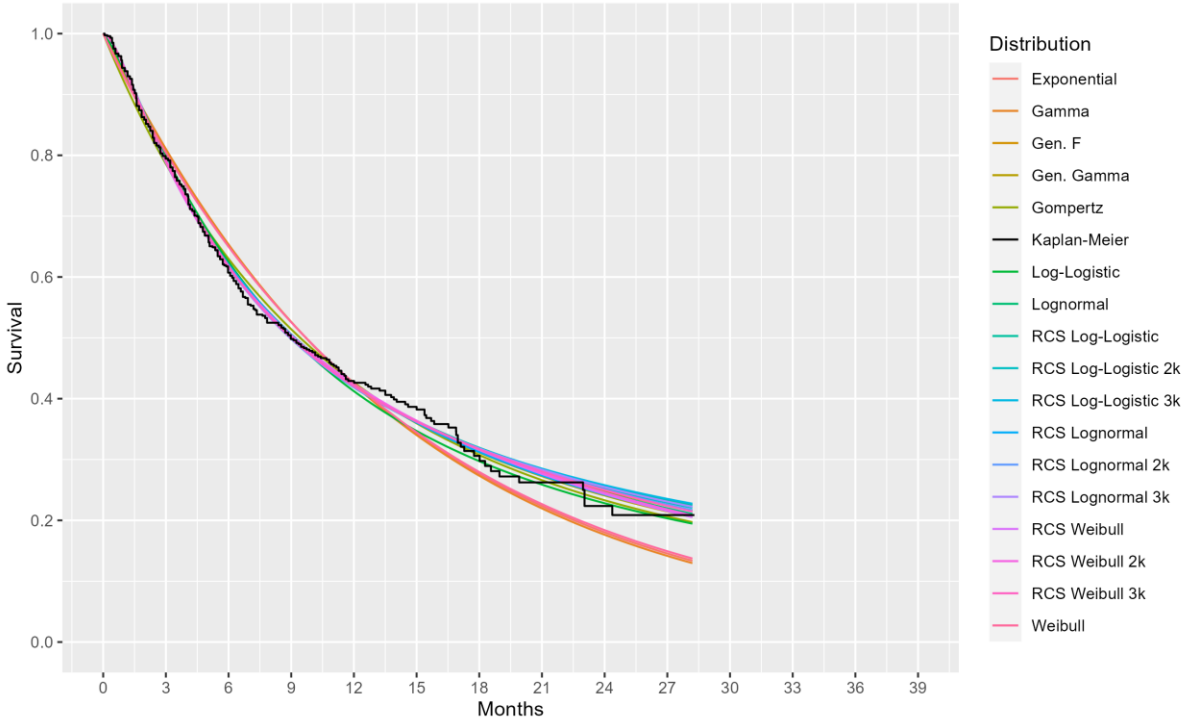
Table 46. IsaPd OS, SACT Predicted survival probabilities at 3, 5, 10, 15 and 30 years

Distribution	Year				
	3	5	10	15	30
Exponential	0.2356	0.0899	0.0081	0.0007	0.0000
Gamma	0.2584	0.1108	0.0138	0.0017	0.0000
Gen. F	0.3470	0.2411	0.1304	0.0850	0.0362
Gen. Gamma	0.3470	0.2411	0.1304	0.0849	0.0360
Gompertz	0.3431	0.2638	0.2177	0.2117	0.2107
Log-Logistic	0.3242	0.2184	0.1184	0.0804	0.0403
Lognormal	0.3504	0.2460	0.1361	0.0904	0.0402
RCS Log-Logistic	0.3545	0.2553	0.1531	0.1106	0.0616
RCS Log-Logistic 2k	0.3293	0.2217	0.1198	0.0812	0.0405
RCS Log-Logistic 3k	0.3472	0.2473	0.1460	0.1045	0.0572
RCS Lognormal	0.3469	0.2416	0.1317	0.0865	0.0376
RCS Lognormal 2k	0.3283	0.2162	0.1062	0.0646	0.0239
RCS Lognormal 3k	0.3446	0.2401	0.1310	0.0862	0.0376
RCS Weibull	0.3309	0.2043	0.0747	0.0315	0.0035
RCS Weibull 2k	0.3119	0.1762	0.0506	0.0167	0.0009
RCS Weibull 3k	0.3326	0.2094	0.0807	0.0359	0.0047

Distribution	Year				
	3	5	10	15	30
Weibull	0.2690	0.1242	0.0200	0.0035	0.0000

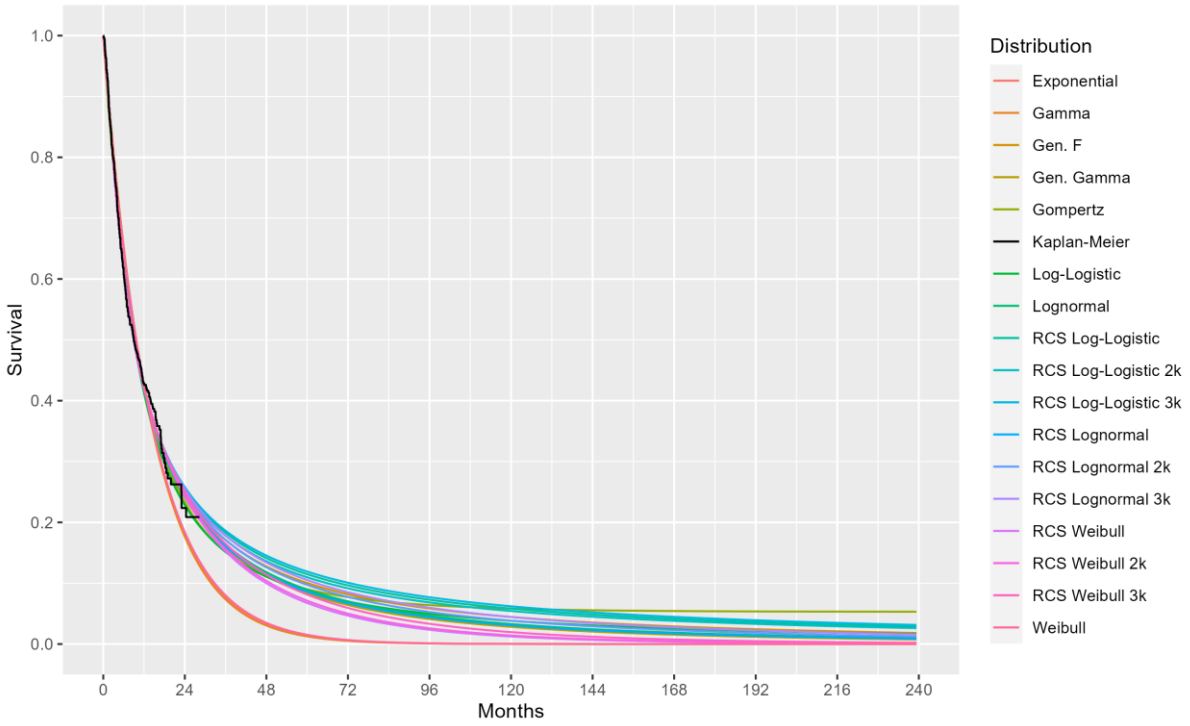
Abbreviations: 2k, two knots; 3k, three knots; IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy.

Figure 41. IsaPd TTD, SACT, independently fitted



Abbreviations: 2k, two knots; 3k, three knots; IsaPd, isatuximab + pomalidomide + dexamethasone; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy; TTD, time to discontinuation.

Figure 42. IsaPd TTD, SACT, independently fitted to 20 year time horizon



Abbreviations: 2k, two knots; 3k, three knots; IsaPd, isatuximab + pomalidomide + dexamethasone; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy; TTD, time to discontinuation.

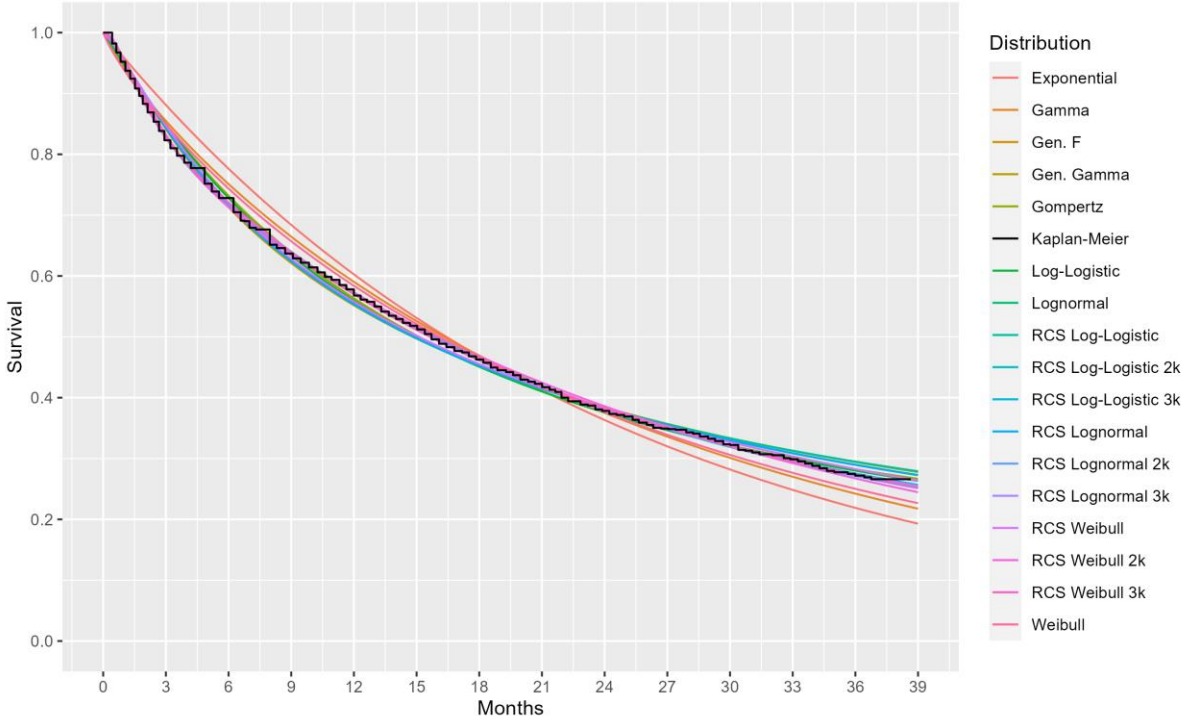
Table 47. IsaPd TTD, SACT Predicted survival probabilities at 3, 5, 10, 15 and 30 years

Distribution	Year				
	3	5	10	15	30
Exponential	0.0765	0.0138	0.0002	0.0000	0.0000
Gamma	0.0732	0.0126	0.0002	0.0000	0.0000
Gen. F	0.1709	0.1004	0.0445	0.0266	0.0104
Gen. Gamma	0.1578	0.0831	0.0283	0.0134	0.0030
Gompertz	0.1516	0.0900	0.0583	0.0539	0.0529
Log-Logistic	0.1513	0.0861	0.0382	0.0234	0.0100
Lognormal	0.1639	0.0895	0.0329	0.0166	0.0043
RCS Log-Logistic	0.1828	0.1148	0.0583	0.0386	0.0188
RCS Log-Logistic 2k	0.1779	0.1097	0.0543	0.0354	0.0168
RCS Log-Logistic 3k	0.1862	0.1191	0.0621	0.0418	0.0209
RCS Lognormal	0.1601	0.0860	0.0308	0.0152	0.0038
RCS Lognormal 2k	0.1713	0.0972	0.0384	0.0204	0.0059
RCS Lognormal 3k	0.1782	0.1052	0.0445	0.0248	0.0079
RCS Weibull	0.1524	0.0675	0.0124	0.0029	0.0001
RCS Weibull 2k	0.1561	0.0713	0.0141	0.0036	0.0001
RCS Weibull 3k	0.1648	0.0813	0.0196	0.0060	0.0003

Distribution	Year				
	3	5	10	15	30
Weibull	0.0800	0.0153	0.0003	0.0000	0.0000

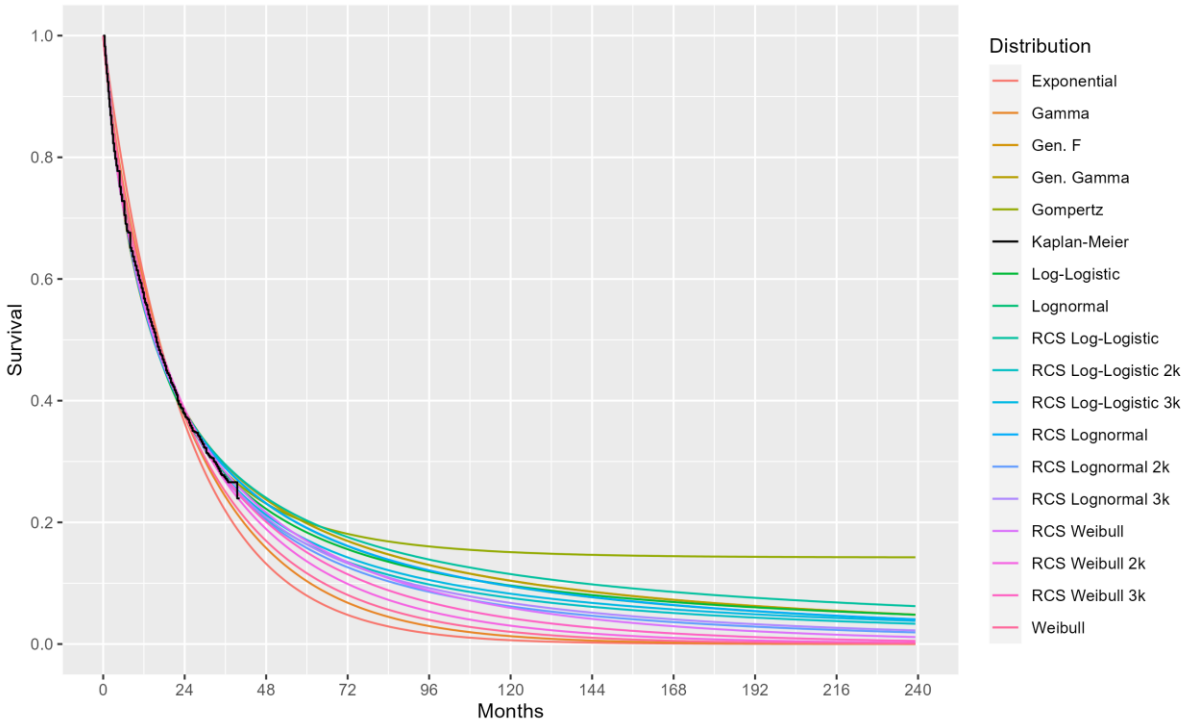
Abbreviations: 2k, 2 knot; 3k, 3 knot; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy dataset; TTD, time to discontinuation.

Figure 43. Daratumumab OS, SACT, independently fitted



Abbreviations: 2k, two knots; 3k, three knots; OS, overall survival; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy.

Figure 44. Daratumumab OS, SACT, independently fitted to 20 year time horizon



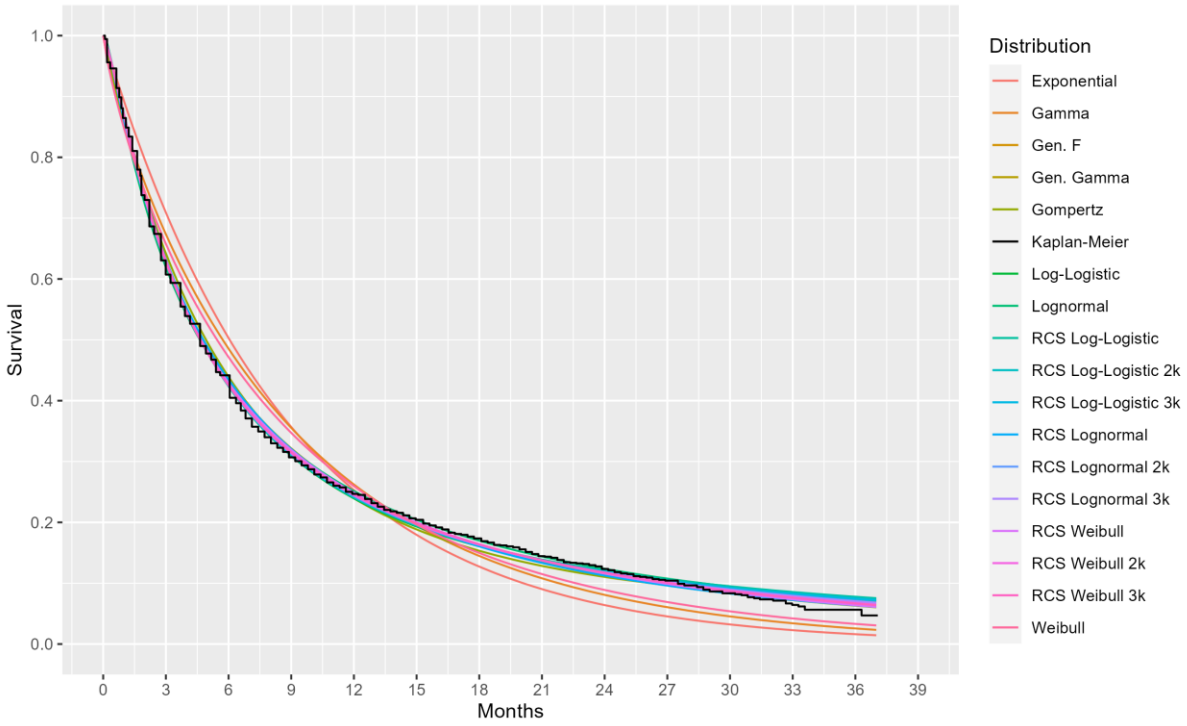
Abbreviations: 2k, two knots; 3k, three knots; OS, overall survival; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy.

Table 48. Dara OS, SACT Predicted survival probabilities at 3, 5, 10, 15 and 30 years

Distribution	Year				
	3	5	10	15	30
Exponential	0.2189	0.0795	0.0063	0.0005	0.0000
Gamma	0.2423	0.1033	0.0129	0.0017	0.0000
Gen. F	0.2943	0.1983	0.1042	0.0674	0.0290
Gen. Gamma	0.2943	0.1982	0.1039	0.0672	0.0288
Gompertz	0.2823	0.2002	0.1511	0.1438	0.1423
Log-Logistic	0.2801	0.1834	0.0962	0.0644	0.0316
Lognormal	0.2895	0.1905	0.0948	0.0586	0.0226
RCS Log-Logistic	0.2950	0.2030	0.1149	0.0805	0.0427
RCS Log-Logistic 2k	0.2716	0.1640	0.0758	0.0470	0.0202
RCS Log-Logistic 3k	0.2754	0.1711	0.0827	0.0526	0.0237
RCS Lognormal	0.2898	0.1909	0.0952	0.0589	0.0228
RCS Lognormal 2k	0.2713	0.1578	0.0619	0.0320	0.0085
RCS Lognormal 3k	0.2742	0.1637	0.0675	0.0363	0.0104
RCS Weibull	0.2827	0.1692	0.0595	0.0248	0.0028
RCS Weibull 2k	0.2673	0.1358	0.0301	0.0077	0.0002
RCS Weibull 3k	0.2731	0.1507	0.0425	0.0141	0.0008
Weibull	0.2502	0.1163	0.0201	0.0039	0.0000

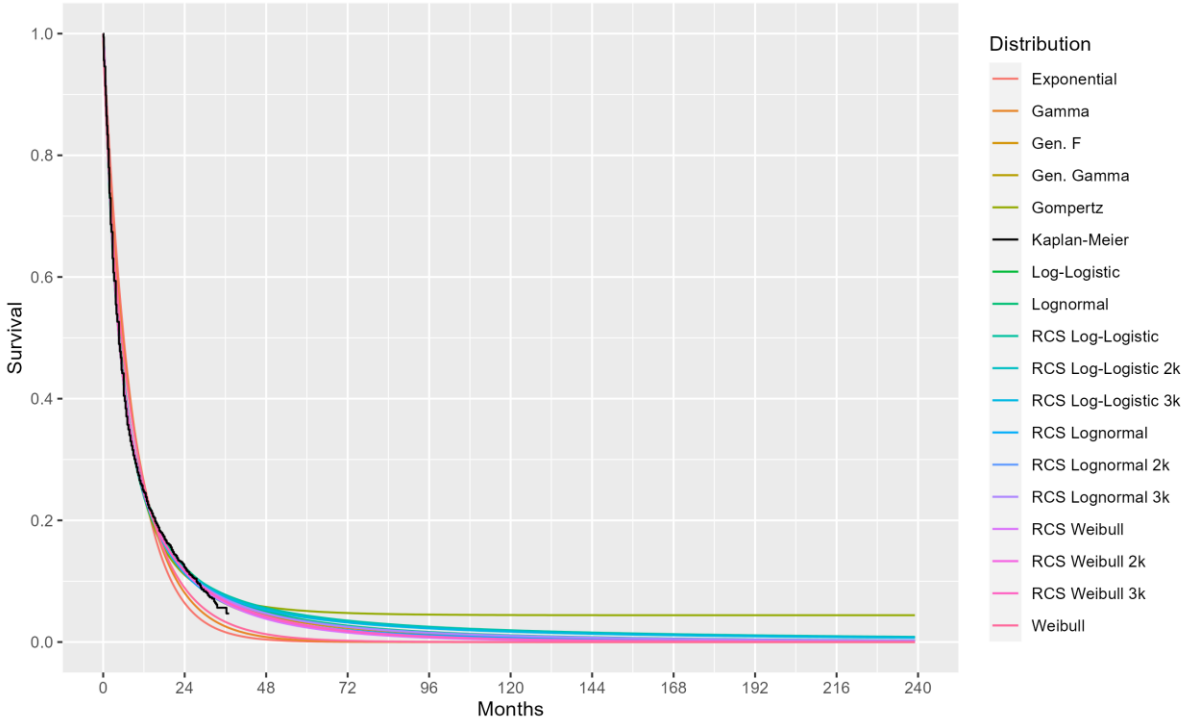
Abbreviations: 2k, two knots; 3k, three knots; OS, overall survival; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy.

Figure 45. Daratumumab TTD, SACT, independently fitted



Abbreviations: 2k, two knots; 3k, three knots; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy; TTD, time to discontinuation.

Figure 46. Daratumumab TTD, SACT, independently fitted to 20 year time horizon



Abbreviations: 2k, two knots; 3k, three knots; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy; TTD, time to discontinuation.

Table 49. Dara TTD, SACT Predicted survival probabilities at 3, 5, 10, 15 and 30 years

Distribution	Year				
	3	5	10	15	30
Exponential	0.0162	0.0010	0.0000	0.0000	0.0000
Gamma	0.0257	0.0027	0.0000	0.0000	0.0000
Gen. F	0.0670	0.0310	0.0094	0.0044	0.0011
Gen. Gamma	0.0630	0.0260	0.0059	0.0021	0.0002
Gompertz	0.0725	0.0510	0.0444	0.0441	0.0441
Log-Logistic	0.0756	0.0419	0.0184	0.0112	0.0048
Lognormal	0.0747	0.0359	0.0111	0.0051	0.0011
RCS Log-Logistic	0.0778	0.0436	0.0194	0.0120	0.0052
RCS Log-Logistic 2k	0.0759	0.0419	0.0182	0.0111	0.0048
RCS Log-Logistic 3k	0.0742	0.0401	0.0169	0.0101	0.0042
RCS Lognormal	0.0635	0.0274	0.0070	0.0028	0.0005
RCS Lognormal 2k	0.0710	0.0340	0.0105	0.0048	0.0011
RCS Lognormal 3k	0.0702	0.0331	0.0099	0.0044	0.0009
RCS Weibull	0.0638	0.0239	0.0035	0.0007	0.0000
RCS Weibull 2k	0.0675	0.0276	0.0050	0.0013	0.0001
RCS Weibull 3k	0.0666	0.0265	0.0045	0.0011	0.0000
Weibull	0.0331	0.0053	0.0001	0.0000	0.0000

Abbreviations: 2k, two knots; 3k, three knots; RCS, restricted cubic splines; SACT, systemic anti-cancer therapy; TTD, time to discontinuation.

c. Repeat (b) based on the RCS models with one, two, and three knots.

Included above in response to B12(b)

B14. Priority. The virtual HTA advisory board Feb 2023 report states that information presented includes *'survival at 5, 10, 15, and 20 years, based on a joint modelling approach using 6 standard parametric distributions'*. Please explain why the experts were not shown unrestricted (independently fitted) survival distributions.

A jointly fitted model was considered appropriate for the advisory board elicitation activity as the Schoenfeld residuals and examination of the log (-log (survival) plots did not support non proportionality of hazards in the presence of more mature data to inform the hazards from the ICARIA-MM trial. The independently fitted survival distributions which had the best statistical fit were nevertheless explored in scenario analyses as part of the NICE submission to demonstrate the impact on the ICER.

B15. Please clarify the software used for the survival extrapolation.

The software used for the survival extrapolation (i.e. curve-fitting) procedures was the R-package Flexsurv (43).

B16. CS p96 states that 'Standard parametric survival analysis consisted of fitting parametric distributions (including exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised gamma distributions) to the observed data from ICARIA-MM'. However, figure 16-21 in Appendix R show that gamma and generalised F distributions were also explored. Please clarify the standard parametric distributions explored in the extrapolation.

Estimates of PFS, PFS on treatment, TTD, and OS for IsaPd and Pd were derived by fitting parametric survival distributions to the individual patient failure time data from ICARIA-MM using Flexsurv, an R package for fully parametric modelling of survival data (43). The following most widely used parametric distributions were considered:

- Exponential;
- Weibull;
- Log-logistic;
- Lognormal;
- Gompertz;
- Gamma
- Generalised gamma;
- Generalised F; and
- Restricted cubic spline (RCS) distributions.

For RCS distributions, Weibull, log-logistic and lognormal distributions used a single knot (plus the two boundary knots, which are always included).

B17. Please clarify if the unrestricted modelling approach is the same as fitting the models to each arm independently.

Yes, the parameters for the distributions are the same, except for the knots chosen for the RCS distributions. When jointly-fitting, the placement of the knots in RCS distributions are assumed to be the same between the arms and will result in the knots chosen in the unrestricted modelling approach differing from what would be estimated if each arm were estimated independently.

B18. For the RCS models, please clarify why only one knot spline models were explored.

Versions of the RCS models with more than one knot were not explored as they generally tend to perform poorly with respect to measures of statistical fit due to penalisation for additional parameters. For practical reasons, number of distributions considered were limited (as per B16). Usually, a good visual fit can be obtained with one of these models with reasonably good fit statistics without overfitting.

B19. Please explain what RCS log-normal, RCS log-logistic and RCS Weibull refer to.

The three RCS distributions refer to the spline-based models included in the R-package Flexsurv with the *flexsurvspline* function (43). These distributions are based on the natural cubic spline survival models defined by Royston and Parmar (44).

Utility analysis

B20. Priority. Please provide the model selection procedure when applying the generalised estimating equations (GEE) regression. For example, the initial model specification, how the final model was chosen, whether AIC and BIC were used for model selection, how the model assumptions were assessed. Please also clarify if any baseline characteristics were adjusted in the regression model and provide justification.

The objective of the model is to calculate utility by health state using all available data and includes adjustments for baseline utility, treatment group and whether the utility reading was near the time the patient died.

As the utility models were estimated using GEE, and this procedure is not a likelihood-based method, the AIC statistic is not available. The quasi-likelihood information criterion (QIC) statistic, a modification of the AIC applies to GEE models and is included in the response to B22. A simplified version of the QIC called the QICu is also included.

The QIC statistic was not used in model selection, rather the model selection in the current re-appraisal was based on the utility modelling approach that was accepted in the original submission where the EAG preferred treatment specific utility in the progression-free health state but not specific utilities for on- versus off treatment in either the progression-free or progressed health state. Therefore, the same approach was taken in this submission.

B21. Priority. Please specify the model equation used for the final model based on the GEE regression approach.

The model equation used for the final utility model in the CS (Model 2) is as below:

Utility = Health state covariate + baseline utility + near death

Models were estimated for different health state categories, and with/without the near-death variable.

B22. Priority. GEE regression models (CS Table 34)

a. Explore a model where there is no treatment effect and provide the goodness-of-fit (AIC and BIC).

The Company maintain that a treatment effect should be included as presented in clarification question B25 as these data have been collected using EQ-5D-5L questionnaire administered in the ICARIA-MM trial; however, to satisfy the request of the EAG an analysis assuming no treatment effect has been explored. In addition to the six previously explored utility models, six utility models with treatment-agnostic health states for PFS (assuming that

there is not treatment effect on PFS state utilities) were generated. The parameterisations and results of these models, labelled as Models 7-12, are presented (Table 50 and Table 51).

It should be noted that the benefit of estimating health state utilities with separate PFS states for IsaPd and Pd is that it accounts for the disutility due adverse events inherent in

the ICARIA-MM HRQoL assessments. This is lost when estimating treatment-agnostic versions of the utility models and hence were not considered appropriate models in the original submission and the current re-review.

Table 50. Treatment non-specific GEE regression models considered for utility value estimation and corresponding goodness of fit statistics

Model	Health state covariate							QIC	QICu
	PFS	PPS	PFS On Tx	PFS Off Tx	PPS On Tx	PPS Off Tx	Near Death		
7	X	X						940.0528	892
8	X	X					X	941.0148	893
9			X	X	X	X		943.9299	894
10			X	X	X	X	X	943.5442	895
11		X	X	X				942.1461	893
12		X	X	X			X	942.9463	894

Abbreviations: GEE, generalised estimating equations; IsaPd, isatuximab + pomalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; PFS, progression-free survival; PPS, post-progression survival; QIC, quasi-likelihood information criterion; Tx, treatment.

Table 51. LSM EQ-5D-3L treatment non-specific utility values based on alternate regression models for 4th line population†

Model	Value	Health state covariate						
		PFS	PPS	PFS On Tx	PFS Off Tx	PPS On Tx	PPS Off Tx	Near Death
7	Estimate	[redacted]						
7	Lower 95% CI	[redacted]						
7	Upper 95% CI	[redacted]						
8	Estimate	[redacted]						
8	Lower 95% CI	[redacted]						
8	Upper 95% CI	[redacted]						
9	Estimate							
9	Lower 95% CI							
9	Upper 95% CI							
10	Estimate							
10	Lower 95% CI							
10	Upper 95% CI							
11	Estimate							
11	Lower 95% CI							
11	Upper 95% CI							
12	Estimate							
12	Lower 95% CI							
12	Upper 95% CI							

† March 2022 data cut. Abbreviations: CI, confidence interval; IsaPd, isatuximab + pomalidomide + dexamethasone; LSM, least square mean; Pd, pomalidomide + dexamethasone; PFS, progression-free survival; PPS, post-progression survival; Tx, treatment.

b. Please provide the goodness-of-fit (AIC and BIC) for the models presented in Table 34.

As noted above, the AIC and BIC statistics are not available for estimation using GEE, as it is not a likelihood-based method. Instead, the QIC and QICu fit statistics are provided (Table 52). As with the AIC and BIC, when using QIC or QICu to compare two structures or models, the model with the smaller statistic is generally preferred (45).

Model 2 is associated with the second lowest QIC and QICu score, with Model 1 associated with the lowest scores, however there is little between each model in terms of statistical fit (1 point by QICu and <3 points by QIC). The distinction between Model 1 and Model 2 is the inclusion of a covariate for patients near death in Model 2. Near death is defined as being within 84 days of death and was estimated from published literature suggesting a quality-of-life decline during the last 3–6 months prior to death in cancer patients (45). In addition, patient data from ICARIA-MM were reviewed prior to the utility estimation and concluded sufficient numbers were available for the 12-week duration to allow for robust estimation of the terminal utility decrement. Therefore, the Company maintains that Model 2 remains an appropriate choice for estimating health state utility values.

Table 52. QIC and QICu for GEE regression models presented in Table 34 of the CS

Utility Model	QIC	QICu
Model 1	945.6392	893
Model 2	947.2266	894
Model 3	951.1216	895
Model 4	952.2002	896
Model 5	953.1277	896
Model 6	952.8944	897

Abbreviations: QIC, quasi-likelihood information criterion.

B23. Priority. The estimated baseline utility was 0.74 for the IsaPd arm, and 0.66 for the Pd arm (CS Table 18). CS p136 states that when calculating the least square mean (LSM), the pooled mean baseline utility values were used. Please clarify how this pooled mean value was incorporated in the LSM calculation and clarify whether baseline utility was included in the regression model as a covariate.

The baseline utility was included as a covariate in all utility models. An overall baseline utility was computed using all patients and used in the LSMEANS statement. For utility models that include the near-death covariate, the LSMEANS statement is evaluated at the baseline utility and for not near-death.

B24. Please clarify how the decrement assumed in the 12 weeks prior to death was incorporated for deaths before 12 weeks for example, in week 2. Would this patient effectively have negative QALYs for the period they were alive?

No, the decrement is only applied to utility values in cycles where a patient is alive and therefore a decrement for the full 12 cycles would not be applied in this case.

B25. Please clarify the biological reasons as to why IsaPd would have a greater utility than Pd. Clarify why the average time in PFS is associated with utility in the PFS state as used to justify setting the utility of daratumumab to the Pd value rather than the value for IsaPd. Explore the impact on the ICER if the utility for daratumumab was set to that of IsaPd.

The transition from doublet-based therapy, such as Pd, to triplet-based combinations like IsaPd in the context of RRMM, can be explained by the recognition that combining therapies that target different biological and sub-cellular pathways, confer a range of anti-myeloma properties. This has been substantiated by pre-clinical data, which revealed that augmenting anti-CD38 treatment (isatuximab) with an IMID-based therapy, significantly enhanced tumour cytotoxicity (46). This biological synergy is a crucial factor behind the utility improvement of IsaPd over Pd.

The greater utility of IsaPd is also linked to the average time in PFS. PFS serves as an indicator of treatment effectiveness and, consequently, its association with utility is pivotal. The ICARIA-MM trial demonstrated a substantial 5.2-month improvement in PFS when compared to Pd in RRMM patients (IsaPd: 11·1 months [95% CI 7·8–13·8] vs Pd 5·9 months [95% CI 4·5–7·9]) (17). In the final data cut (March 2022) in 4th line patients, median PFS was prolonged in the IsaPd arm (12.39 months [95% CI; 7.425, 27.663]) compared with the

Pd arm (6.54 months [95% CI; 4.468, 10.086]) (3). The benefit derived from the prolonged PFS is indicative of IsaPd's therapeutic advantages, which translates into enhanced utility. This gain in PFS, over an extended 24-months additional follow-up, strengthens the justification for setting the utility of daratumumab at the Pd value rather than IsaPd's value. The availability of IsaPd to patients and clinicians via the CDF has been favourably received (47). The evidence presented in the CS highlights that IsaPd has a higher response rate which lasts longer than other available treatment options at this line of therapy. As noted in the CS, currently, SoC therapy is associated with lower response rates, shorter duration of response and poorer PFS outcomes compared with IsaPd. Clinicians opt to use the treatment which offers the longest period of PFS (47), an outcome that is highly valued by end-stage patients- reflected in the sustained uptake of IsaPd in the CDF, despite the availability of daratumumab monotherapy and Pd.

Furthermore, it is important to note that the patient-reported outcomes from ICARIA-MM, specifically health-related quality of life (HRQoL) assessments, indicated that the addition of isatuximab to Pd preserved the quality of life in RRMM patients whilst improving efficacy. The HRQoL was largely maintained throughout the duration of treatment (15). The maintenance of HRQoL is partially attributed to clinically meaningful improvement in pain management and the delay in physical functioning decline with IsaPd vs. Pd. Notably, the time to the first significant deterioration (≥10 points) in the global health status and role functioning domains was more favourable for IsaPd compared to Pd, with a statistically non-significant hazard ratio. This evidence was acknowledged by the Institute for Quality and Efficiency in Health Care (IQWiG) (48), and was considered a minor added benefit for IsaPd. These enhancements in quality of life are likely key contributors to the observed improvement in utility, particularly within the EQ-5D domains, for IsaPd compared to Pd in the pivotal trial. These factors collectively contribute to IsaPd's higher utility, making it a preferable treatment option.

Importantly, no direct head-to-head trials have directly compared IsaPd to daratumumab monotherapy or Pd to daratumumab monotherapy in terms of effectiveness or HRQoL. A combined analysis of two single-arm studies, SIRIUS and GEN501, revealed that the median PFS for the overall population was 4.0 months (95% CI, 2.8-5.6 months) (49) after a median follow-up of 20.7 months. However, HRQoL data for these studies were not available. Another analysis included patients from the UK, Spain, Italy, and Russia receiving daratumumab monotherapy through an early access treatment protocol. This study reported minimal changes from baseline in all patient-reported outcome domains, as measured by various instruments. The changes from baseline were generally close to zero (33). From these data it could be inferred that IsaPd may offer advantages over daratumumab monotherapy in terms of PFS, and the preservation of HRQoL in the ICARIA-MM trial lends support to IsaPd's utility being seen as superior.

In the non-inferiority trial COLUMBA, the comparison between subcutaneous and intravenous formulations of daratumumab monotherapy was explored however, no equivalent HRQoL data were collected.

In summary, while there's a dearth of head-to-head studies and comparable objective utility values for daratumumab monotherapy, the biological synergy of this triplet regimen, along with its superior PFS and preservation of HRQoL, contribute to the argument that IsaPd

offers greater utility than Pd or daratumumab monotherapy. This cumulative increase in total health-related utilities, such as quality of life, is a strong rationale for favouring IsaPd in the treatment of RRMM. Nevertheless, a scenario assuming equivalent utility value in the PFS state for IsaPd and daratumumab monotherapy has been tested and results in a minor increase in the base case ICER from £141,251 to £146,401 (Table 53).

Table 53: Base case ICER vs daratumumab monotherapy, equivalent PFS utility value to IsaPd

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Daratumumab	[redacted]	[redacted]	[redacted]	-	-	-	-
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£146,401

Abbreviations: ICER, incremental cost-effectiveness ratio; IsaPd, isatuximab + pomalidomide + dexamethasone; LYG, life years gained; PFS, progression-free survival; QALYs, quality-adjusted life years.

Section C: Textual clarification and additional points

C1. Under CS Figure 39 it is stated that '*Most of the distributions yield projections of TTD for IsaPd of around 15% by 10 years*'. Is this a typo as this does not appear to be supported by Figure 41?

The statement should read "*Most of the distributions yield projections of TTD for IsaPd of around **5%** by 10 years, apart from the Gompertz and RCS Weibull.*" and is supported by Figure 41 in the CS (Document B).

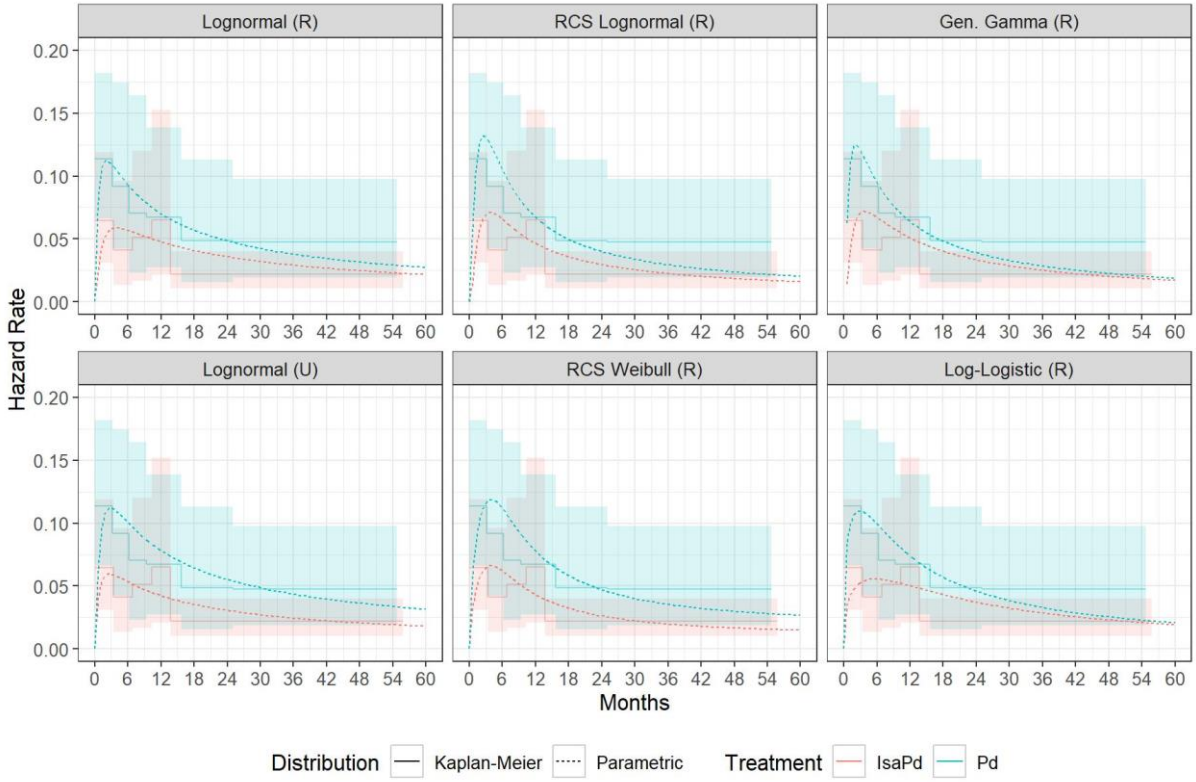
C2. Above Figure 42 there is text that states 'TTD for IsaPd that are approximately 20% at six years, 10% at 14 years, and ~6% at 20 years' Is this a typo?

This statement should read as follows: "*TTD for IsaPd are approximately **9% at 5 years**, **3% at 10 years**, and **1% at 20 years***".

C3. CS Figure 12 hazard rate for OS appears to be identical to Figure 17 hazard rate for PFS. Is this a typo?

The corrected hazard rate for PFS for the 4th line population from ICARIA-MM are presented in Figure 47 (below); the hazard rate for OS remains correct in the CS.

Figure 47: Hazard rates for parametric survival distributions fit to PFS for the 4th line population from ICARIA-MM, by randomised treatment



Abbreviations: IsaPd, isatuximab + pomalidomide + dexamethasone; OS, overall survival; Pd, pomalidomide + dexamethasone; R, restricted; RCS, restricted cubic spline; U, unrestricted.

C4. On CS p154 there is a reference to Hernandez et al, Should this be M Hernández Alava, S Pudney, A Wailoo (2022) Estimating EQ-5D by Age and Sex for the UK**. NICE DSU report rather than the reference in 161, which relates to EQ-5D mapping?**

The correct citation should be: Hernandez-Alava M, Pudney S, Wailoo A. Estimating EQ-5D by age and sex for the UK. NICE Decision Support Unit (DSU) report. 2022. Available at: https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d (last accessed October 2023) (50).

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [Review of TA658] [ID4067]

Patient Organisation Submission

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. [Please note that declarations of interests relevant to this topic are compulsory].

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.

NICE National Institute for Health and Care Excellence

About you

<table>
<tr><td>1.Your name</td><td>Caroline Donoghue</td></tr>
<tr><td>2. Name of organisation</td><td>Myeloma UK</td></tr>
<tr><td>3. Job title or position</td><td>Senior Policy Officer</td></tr>
<tr><td>4a. Brief description of the organisation (including who funds it). How many members does it have?</td><td>Myeloma UK is the only organisation in the UK dealing exclusively with myeloma and its associated conditions. 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 are not a membership organisation 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.</td></tr>
<tr><td>4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]
If so, please state the name of the company, amount, and purpose of funding.</td><td>The table below shows the 2022 income from the relevant manufacturers. Funding is received for a range of purposes and activities namely core grants, project specific work including clinical trials, and gifts, honoraria or sponsorship.
<table>
<tr><th>Name of Company</th><th>Grants and project specific funding</th><th>Gifts, Honoraria and Sponsorship</th><th>Total (£)</th></tr>
<tr><td>Abbvie</td><td></td><td>10,000</td><td>10,000</td></tr>
<tr><td>Amgen</td><td>25,000</td><td></td><td>25,000</td></tr>
<tr><td>Celgene-BMS</td><td>20,000</td><td>15,000</td><td>35,000</td></tr>
<tr><td>GSK</td><td>20,444</td><td></td><td>20,444</td></tr>
<tr><td>Janssen</td><td>25,000</td><td>180</td><td>25,180</td></tr>
<tr><td>Sanofi</td><td></td><td>48,980</td><td>48,980</td></tr>
<tr><td>Takeda</td><td>40,000</td><td>17,000</td><td>57,000</td></tr>
</table></td></tr>
<tr><td>4c. Do you have any direct or indirect links</td><td>No</td></tr>
</table>

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information included in this submission came from the myeloma patients and carers we engage with through our research and services programmes, including: • A patient survey designed to understand the patient experience of being treated with IsaPd. 57 patients treated with isatuximab (Sarclisa®) in combination with pomalidomide (Imnovid®) and dexamethasone (IsaPd) completed the survey. • A multi-criteria decision analysis study of 560 myeloma patients. The study, funded by Myeloma UK and run by the European Medicines Agency (EMA) and the University of Groningen, explored patient preferences for different benefit and risk outcomes in myeloma treatment. • 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 someone with the condition?	Myeloma is a highly individual and complex cancer originating from abnormal plasma cells in the bone marrow. There is no cure, but treatment can halt its progress and improve the quality of life. The complications of myeloma can be significant, debilitating and painful; and include severe bone pain, bone destruction, kidney damage, fatigue and a depleted immune system that can lead to increased infections. In a survey of 1324 patients and carers, 72% of respondents reported that their myeloma had a high or moderate impact on their quality of life. ***"Myeloma has had a major impact on my quality of life. No day is the same as you can wake up and find you are in chronic pain and unable to do anything for yourself and have to rely on your carers which has a really negative effect on your mental health. Some of the simplest tasks become impossible to undertake such as going to the bathroom or making a cup of tea… things we take for granted."*** Myeloma is a relapsing and remitting cancer. Relapse completely disrupts the lives of patients and their families. Their symptoms increase (e.g., pain, fatigue). Hospital visits and tests increase. Patients also must switch treatments and adjust to different side effects and new routines for hospital visits/treatment administration. Relapsed patients, the population covered in this appraisal, often experience a more significant disease burden. They face a worse prognosis and a higher 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] Each additional line of treatment is associated with worse outcomes; remission times decrease and side effects increase. Treatments often become less effective and harder to tolerate with every relapse. Over time, myeloma evolves, becoming more resistant to treatment, and patients get older, frailer and have more comorbidities.[2] The individual and heterogeneous nature of myeloma means that some patients may respond to or tolerate treatment well, and others may not. In addition, myeloma evolves and becomes resistant to treatment. Therefore, it is essential to have a range of treatment options with different mechanisms of action at all stages of the myeloma pathway. ***"The more options the better chance of having one work and be compatible. Two previous ones have failed, or I reacted badly to."*** ***"It takes away the pressure of knowing that myeloma is incurable but treatable. Reducing the number of lines reduces one side of that equation."***

	"Relief. Myeloma is currently incurable, so a variety of available strategies/ options gives me and my partner some hope and time." Living with myeloma is often extremely physically and emotionally challenging for carers, and family members. They are affected in many ways because of both caring and dealing with the day-to-day implications of myeloma. Many in this situation mention changes in their social life, relationships, income, and wider family dynamics. 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% of those in work had been unable to work or had to retire early to care for the person with myeloma - 84% always put the needs of their relative or friend with myeloma before their own - Only 42% of carers were not given enough information at diagnosis about how myeloma may affect them[3] ***"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."*** ***"Sometimes it's tiring. Sometimes I feel sad. Sometimes I think about all the hours I have spent at the hospital and how I might have used that time otherwise. But it's all the price of love."***

[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
[2] Yong, K., et al.
[3] A Life in Limbo: A Myeloma UK research report on the experience of myeloma carers in the UK 2016: https://www.myeloma.org.uk/documents/a-life-in-limbo/

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 feel fortunate that although myeloma is incurable, it is treatable in most cases. However, patients and carers, especially those who have already experienced relapse, are acutely aware that the range of treatment options and the chance of deep responses with long remissions decreases every time they relapse. They know about treatment resistance and that an effective treatment will stop working at some point. Understandably, this can cause a great deal of worry for myeloma patients, as well as their carers and families, as there is uncertainty about the future, whether the new treatment will work and how well they will tolerate and fear of reaching the 'end' of treatment options for their cancer. ***"Very important to know that if one treatment fails, there are others available. Peace of mind."***. ***"[Accessing IsaPd was] really important as I was concerned about the narrowing of my options coming onto fourth line.*** Multiply relapsed/refractory patients follow the development of innovative treatments and perceive aspects of the current treatment offer to be less than optimal. **"Some of the other remaining options are not so good."**

8. Is there an unmet need for patients with this condition?	There is a clear need for novel, effective combination treatments at the third and fourth lines. Myeloma is a heterogenous cancer comprised of several different subclones. Therefore, combination treatments with complementary mechanisms of action are preferred. Relapse is caused by resistance to existing treatment. Myeloma remains incurable, and even after successful treatment, almost all patients eventually become resistant to existing treatment. Treatments that have worked well at previous lines are no longer effective. Patients with relapsed or refractory myeloma are all too familiar with this scenario. Their disease is resistant to most existing treatments, and innovative treatments are required to control their myeloma. New drugs and treatment combinations are urgently needed to overcome treatment resistance. The absence of lenalidomide in this triplet combination is a significant patient benefit. There is an increase in lenalidomide refractory patients at the 3rd and 4th line following the approval of lenalidomide maintenance and its increased use earlier in the pathway. Combination treatments are more effective than monotherapies. Myeloma has genetically distinct clones, and the variation in treatment susceptibility between clones is one of the main causes of relapse and treatment resistance in myeloma. Therefore, it is best practice to use combination treatments containing multiple drugs with different mechanisms of action to treat myeloma with triplet and quadruplet combinations are now standard therapy in myeloma. In our patient survey, 77% of patients who received Isa-Pd told us they were not offered alternative treatment options. The main alternative treatment option offered was daratumumab monotherapy which several patients saw as a sub-optimal option compared to Isa-Pd. ***"I was offered dara, I chose isaPd as if was my consultants preferred* choice**."

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We know from our research that patients value treatments which put their myeloma into remission for as long as possible, prolong their life and allow them to enjoy a normal day-to-day life. The ICARIA-MM clinical showed this triplet combination delivers these benefits. It improved responses rates (60.4% vs 35.3%), lengthened remissions times (11.5 months vs 6.5 months) and increased overall survival (24.6 months vs 17.7 months) compared to the current standard treatment, pomalidomide and dexamethasone. Our patient survey also showed that patients felt the treatment delivered these benefits, with 86% of patients rating their overall experience of IsaPd as positive or very positive. Patients often attributed positive experiences to treatment effectiveness, manageable side effects and improved quality of life. ***"The drug combination is controlling my light chain levels very effectively. Side effects are tolerable. Only involves a hospital appointment for treatment every 2 weeks."*** ***"I have been able to continue to live a comparatively good life. I have had no side effects and my bloods remain stable to date."*** ***"Well tolerated and gave me a relatively straightforward 15 months more with my family"*** Most patients found the ongoing treatment side effects manageable, with 59% of patients saying that treatment side effects did not impact them or stop them from completing normal daily activities. Patients also expressed their relief at having a treatment that allowed them to enter and maintain a period of remission, some lasting several months. Remission is an important outcome for patients and their families with 81% patients saying remission improved their quality of life. ***"I can do my normal range of activities - go walking, rock climbing, socialising , and do all my house work . I also work part time."*** ***"I am in good health (apart from myeloma) and means I can almost stop worrying about this disease and get on with life and look long term instead of short term."***

	The patient survey also highlighted the importance of having access to novel, combination treatment at later lines of the myeloma pathway, as serval patients told us that IsaPd was the only treatment they had responded to following serval ineffective or intolerable lines of treatment. ***"This is the only line of treatment that has brought down my paraproteins"*** ***"It has given me a lifeline when nothing else seemed to be working for me"*** Patients also desire treatments with minimal negative impact on quality of life, particularly those with as few side effects as possible and of low severity. Overall, IsaPd improved or maintained quality of life of most patients with 35% of patients saying IsaPd improved their quality of life and 51% reporting that their quality of life stayed the same. Furthermore, in our engagement with patients across the myeloma pathway many have described isatuximab as a "kinder" treatment to take which does not increase toxicity in combination with other treatments. ***"It is much better in that I have a very good quality of life. I have had 2 STCs which took a while to recover from and I have suffered side effects from the Dex on every other treatment I have had."***

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	In our treatment survey, 39% of patients said that the treatment side effects partially stopped them from completing everyday activities. The side effects mentioned the most our patient survey were fatigue or gastrointestinal issues. Despite these side effects, the overall rating for Isa-Pd was largely positive. Patients often accept varying levels of toxicity if a treatment delivers good survival benefits. The mode of administration, twice monthly trips to the hospital for an infusion, was considered a disadvantage by some patients. The level of inconvenience differed among patients, with 37% rating the mode of administration as very positive, 39% as positive, 21% as neutral and 3% as negative. Negative experiences appeared to be dependent on previous treatment experiences and ease of getting to the hospital. ***"Having survived 7yrs on a Revlimid trial with only one hospital visit a month plus being able to take the drug orally IsaPd feels intrusive"*** ***"I have to go for an infusion at the hospital every 2 weeks. This can take 3-4 hours at least. I have to be cannulated, then after the pre-meds I have to wait for half an hour. The infusion is 1 hour 15 minutes + 15 minutes saline before and after. I would prefer to have the treatment by injection (or tablets would be even better) if it were possible, which would mean less time spent at the hospital."*** ***"I have Isatuximab intravenously every fortnight, which suits me better than having to go to the hospital every week for treatment which was what I was doing before, and I take pomalidomide and dexamethasone as tablets."*** Some patients see regular hospital visits as an advantage. ***"Fortnightly infusion keeps me in touch with the Cancer Centre and the magnificent staff/consultants, whilst the bulk of my medication is under my direct control, at home."*** The use of dexamethasone in the combination is considered a disadvantage by several patients. Dexamethasone is commonly used in myeloma treatment combinations, including the main comparator treatment (pomalidomide and dexamethasone). The mood swings, irritability and mania caused treatment is challenging for patients and their families. 56% of patients who said their treatment dosage was adjusted had a reduction in dexamethasone. ***"Like other treatments the family understand there is some side effects which are not limited to IsaPd e.g., fatigue and low mood, which I believe from experience of this and previous treatments the Dex is a significant contributor to".***

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.	Patients who are refractory to lenalidomide and proteosome inhibitors. Proteasome inhibitors (PI) and immunomodulatory (IMiD) drugs are the most 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. [4]

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

[4] 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*)

Other issues

13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• 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. • 86% of patients rated their overall experience of IsaPd as positive or very positive. They often attributed positive experiences to treatment effectiveness, manageable side effects and improved quality of life. • Patients value the efficacy of the treatment above any inconvenience in the method of administration and consider the side effect profile to be tolerable. • Clinical trial data and insights from our patient survey confirm that IsaPd can deliver benefits which are most important to patients longer remission times, improved overall survival and quality of life. The higher response rate is also important to patients and delivers benefits in terms of certainty.

Thank you for your time.

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Single Technology Appraisal

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [Review of TA658] [ID4067]

Clinical expert statement

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **13 December 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Part 1: Treating relapsed or refractory multiple myeloma after three prior therapies, including lenalidomide and a proteasome inhibitor and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Neil Rabin and Dr Jonathan Sive
2. Name of organisation	UK Myeloma Society
3. Job title or position	Consultant Haematologist and Advocacy Lead UKMS (NR) Consultant Haematologist and Executive Member UKMS (JS)
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 multiple myeloma? ☐ A specialist in the clinical evidence base for multiple myeloma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

8. What is the main aim of treatment for relapsed or refractory multiple myeloma after three prior therapies? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Prolonged survivorship with improved quality of life through minimal treatment-related toxicity and maximal impact associated with limited disease-related morbidity.
9. 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)	Achievement of at least a Partial Remission(>50% reduction in blood-borne markers), optimally better than a Very Good Partial Remission (>90% reduction in blood-borne markers) that is sustained and associated with improved quality of life.
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory multiple myeloma after three prior therapies?	There are many unmet needs in caring for patients with myeloma, relevant to this HTA. Myeloma remains an incurable illness associated with significant morbidity. Advances in therapy-related survivorship with Isatuximab Pomalidomide allows for disease control, reduced health burden and prolonged survival compared to current treatments.
11. How is relapsed or refractory multiple myeloma after three prior therapies, including lenalidomide and a proteasome inhibitor currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The treatment "pathway" is delineated by multiple, non-linked NICE HTA decisions, including drug combination availability through the CDF. This has led to a some-what rigid artificial pathway that limits individualised patient treatment decision and clinical judgment in many cases. Consequentially there are differences of opinion from what we (the professionals) wish to do versus what we are allowed to do (dictated by NICE HTAs). Add to this the dogma of "one size does not fit all" and myeloma therapy is a complicated landscape that is well placed to become the beacon of personalised anti-cancer medicine. The current technology under consideration allows patients who are sensitive to an anti-CD38 therapy to receive this is combination with a potent immunomodulatory agent.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The proposed regimen is a triplet, which will replace an all oral doublet. The third drug (Isatuximab) is a parentally administered drug that is currently only delivered in a hospital basis. As such, there will be pharmacy preparation impact

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	as well as impact on oncology day units. There is unlikely to be any investment though capacity in day units will need supporting
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	We fully expect the technology to improve significant disease control, limiting disease-related morbidity and improving survivorship myeloma patients with relapsed/refractory disease. This will translate into meaningful gains in quality of life for our patients.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	We expect all patients to gain benefit from this technology.
15. 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)	There is no issue about regimen delivery, as most units are familiar with Isatuximab delivery now for over 2 years whilst it has been made available through the Cancer Drugs Fund.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Only standard of care stop/start rules with no extra investment needed.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	We think the health-related benefits are mostly captured.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This technology improves disease control for patients with myeloma with relapsed/refractory disease, limiting disease-related morbidity and improving survivorship.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Isatuximab is delivered as an iv infusion. There is an increase risk of neutropaenia and infection when given in combination with Pomalidomide (compared to Pomalidomide alone). Patients who experience this may need prophylactic antibiotics and use regular GCSF. There is no other additive effect of Isatuximab on Poamlidomide/Dexamethasone related side effects seen in standard of care.
20. Do the clinical trials on the technology reflect current UK clinical practice?	There has been widespread adoption of Isatuximab Pomalidomide Dexamethasone in the UK. This has been made available through the Cancer Drugs Fund.

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Outcomes reported in the ICARIA trial (response rate, PFS, OS and health related quality of life outcomes) are all relevant to current UK clinical practice.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA427 and TA783?	No
23. How do data on real-world experience compare with the trial data?	UK published real world data matches the published ICARIA data. A large dataset has been published by the Oxford Myeloma Group that demonstrates equivalent response rate, PFS and OS to the ICARIA trial. Importantly this relates to where this technology would be used. (Djebbari et al, Hemasphere. 2022 May 26;6(6):e738. doi: 10.1097/HS9.0000000000000738. eCollection 2022 Jun)
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	No

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Isatuximab Pomalidomide Dex leads to improved survival in relapsed/refractory myeloma

Isatuximab Pomalidomide Dex leads to Improved disease control and quality of life in relapsed/refractory myeloma

Widespread adoption of Isatuximab Pomaliodmide Dex, via Cancer Drugs Fund

Isatuximab Pomalidomide has manageable side effects

Significant unmet need in myeloma patients with relapsed/refractory disease

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Single Technology Appraisal

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [Review of TA658] [ID4067]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with multiple myeloma or caring for a patient with multiple myeloma. The text boxes will expand as you type.

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Patient expert statement

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [Review of TA658] [ID4067]

Part 1: Living with this condition or caring for a patient with relapsed or refractory multiple myeloma

Table 1 About you, relapsed or refractory multiple myeloma, current treatments and equality

1. Your name	
2. Are you (please tick all that apply)	☐ A patient with multiple myeloma? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with multiple myeloma? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Myeloma UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

Patient expert statement

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with relapsed or refractory multiple myeloma? **If you are a carer (for someone with relapsed or refractory multiple myeloma) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for relapsed or refractory multiple myeloma on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for relapsed or refractory multiple myeloma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of isatuximab with pomalidomide and dexamethasone over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does isatuximab with pomalidomide and dexamethasone help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of isatuximab with pomalidomide and dexamethasone over current treatments on the NHS please describe these. For example, are there any risks with isatuximab with pomalidomide and dexamethasone ? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from isatuximab with pomalidomide and dexamethasone or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering relapsed or refractory multiple myeloma and isatuximab with pomalidomide and dexamethasone? Please explain if you think any groups of people with this condition are particularly disadvantage	

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13. Are there any other issues that you would like the committee to consider?	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

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Patient expert statement

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Part 1: Living with this condition or caring for a patient with relapsed or refractory multiple myeloma

Table 1 About you, relapsed or refractory multiple myeloma, current treatments and equality

1. Your name	Nigel Spencer
2. Are you (please tick all that apply)	☒ A patient with multiple myeloma? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with multiple myeloma? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Myeloma UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

Patient expert statement

	☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with relapsed or refractory multiple myeloma? **If you are a carer (for someone with relapsed or refractory multiple myeloma) please share your experience of caring for them**	I was diagnosed with Kappa Light Chain Myeloma in July 2018. At the time of diagnosis I had 4 wedge vertebral fractures and a fractured sternum which required me to wear a brace for 4 months. I initially took part in the Cardamon trial but was taken off this in week 2 due to suspected thrombotic microangiopathy caused by Carfilzomib. I then underwent 6 cycles of Bortezomib/Thalidomide/Dexamethasone prior to a Stem Cell Transplant in late June 2019. I relapsed in April 2020 and was treated with Ixazomib/Lenalidomide/Dexamethasone until a further relapse in November 2021. I have been on Isatuximab/Pomalidomide/Dexamethasone since December 2021 and my light chain results have been in normal ranges since Cycle 2. My treatment has taken place at Enfield Chase Farm with the exception of my Stem Cell Transplant which took place at UCLH and treatment of my fractures which took place at the Royal Orthopaedic Hospital. Treatment at all of these has been excellent. I have been fortunate in that I have found side-effects from all treatments (except Carfilzomib) manageable to varying degrees and have been able to maintain a good quality of life. I was able to carry on my job as a senior manager at the British Library team through the first three lines of treatment continuing to perform all elements of a demanding role without any need to make allowances for my condition or treatment. My role did allow me the scope to work at home if needed but in many ways this was one of the most productive periods of my 39-year career at the Library. I retired in January 2022. My reasons were personal and professional and I would have been physically and mentally able to carry on working had I needed to and Library.

	Since retirement have carried out voluntary work for a community centre in Camden. I have been able to enjoy a full family life. Since I have been on Isatuximab we have had holidays in Cyprus, Paris and Austria as well as breaks in the UK and we frequently attend concerts in clubs in London and I have been able to attend sporting events, like watching Brighton and Hove Albion. There are no external physical signs that I have a serious condition. No-one visiting my house would be aware that I had this condition unless they took a look in my medicine cupboard. I am fully physically mobile and able to exercise, drive and carry all day-to-day activities. The only area where I must take care is when lifting heavy items as my bones are still likely to have some weakness. However mental well-being has presented a challenge as my sense of a future is so different from that of a healthy person. Thankfully, to date I have been able to maintain a positive outlook. This has been due to a supportive family and, when I was working, a supportive work-environment but it has required constant vigilance and management much of which has involved an awareness of the triggers that can lead to anxiety and depression and my ability, so far, to frame my situation in as positive way as possible. The fact that I have been able to continue to contribute to the lives of others through my work, volunteering and being a family member has also been a major factor. I have been sufficiently independent that my family have been able to continue to lead their personal and professional lives without having to adapt their lives to care for me which I believe has, in turn, helped them to live with the impact on their mental well-being that having a close relative with Myeloma can have.

	The element that has been most challenging is that, as I have worked my way through treatments, the stakes have become higher as future options are reduced. The anxiety experienced when receiving test results caused by the knowledge that relapse could bring me nearer to the end of treatment options can obviously be reduced by the availability of a greater range of treatment options. This is why having a wide range of such options impacts not only the physical but mental health of Myeloma patients and their carers.
7a. What do you think of the current treatments and care available for relapsed or refractory multiple myeloma on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	The current treatments have enabled me to have a much more fulfilling life than seemed possible when I was diagnosed 5 and a half years ago. I am extremely grateful for their existence and to all those that have enabled me to benefit from them. With the exception of Carfilzomib,to which I had a negative reaction, all the treatments listed above have been effective in controlling my disease for differing periods of time with manageable side-effects. My stem cell transplant was the period in which I experienced the worst side effects. I had a day of extreme nausea shortly following receiving Melphalan and caught an infection 7 days after the transplant. However, I recovered quickly, was discharged two weeks after the transplant and returned to work in 2 and a half months. However my main problem has been that my Myeloma has become resistant to all treatments so far with the exception of Isatuximab which has provided the longest period in which I have had no active disease. At no point have I have asked my consultant about my life expectancy but I was told, at the time when I relapsed from my Stem Cell Transplant, that unless there was a major development in the types of treatments available, I would require treatment for the rest of my life.

	I am aware of the experiences of other patients through the discussion on the UK Myeloma Support group on Facebook. Whilst my experiences are similar to those of many contributing group members others experience more debilitating side-effects than I have from all the majority of treatments that I have had. This is particularly the case with a stem cell transplant when many experience extended recovery periods. In the case of Isatuximab the majority of patients that have posted appear to have similar experiences to me.
8. If there are disadvantages for patients of current NHS treatments for relapsed or refractory multiple myeloma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I have been fortunate in that I have tolerated most treatments well. My induction chemotherapy had an impact on my energy levels which I was able to work around. In the weeks following my stem cell transplant I experienced digestive issues and I also experienced these to a lesser extent with Ixazomib/Lenalidomide/Dexamethasone. I have experienced no significant few side effects with Isatuximab with the exception of energy fluctuations when I was on a higher dose of Dexamethasone in the first few months of the treatment. The treatments have involved varying requirements to attend hospital appointments for treatments and tests. I have had no difficulty in adapting my schedule to enable me to attend these. It is obviously more convenient when a treatment can be taken at home than when a hospital visit is required. If a hospital visit is required, then an injection is less time- consuming than an infusion. A treatment visit for Isatuximab takes approximately four hours every two weeks. Any inconvenience this may cause is more than compensated for by feeling better for the other 13 and a half days.
9a. If there are advantages of isatuximab with pomalidomide and dexamethasone over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	The primary advantage of this treatment has been the absence of side-effects which has given me a good quality of life and the ability to chose the type of life I wish to lead. The impact of this has been that, I hope, the lives of others have been enhanced, such as family members and those who have benefitted from my efforts at work and in volunteering.

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does isatuximab with pomalidomide and dexamethasone help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Overall I feel that I have been able to experience autonomy, agency and the ability to make choices in my own life to a greater extent with Isatuximab than with other treatments and this for me is the most important as it impacts both my physical and mental well-being and that of my family. The treatment has also been the most effective in controlling my disease. At no point from my induction chemotherapy to my relapse from Ixazomib had my Kappa Light Chains been lower than 40. From Cycle 2 of Isatuximab they and the ratio to Lambda Light Chains have been within normal ranges. Other treatments also had an impact on platelet levels and this has not been the case with this treatment.
10. If there are disadvantages of isatuximab with pomalidomide and dexamethasone over current treatments on the NHS please describe these. For example, are there any risks with isatuximab with pomalidomide and dexamethasone ? If you are concerned about any potential side effects you have heard about, please describe them and explain why	None of which I am aware.
11. Are there any groups of patients who might benefit more from isatuximab with pomalidomide and dexamethasone or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Immunotherapy may be one of the few treatment options for patients that have not responded well to proteasome inhibitors. This could be because of the failure of these treatments to control the disease or because of negative side-effects. I am unaware from my own experiences or through discussions I have read on the UK Myeloma Support group on Facebook of any patient groups for whom treatment with Isatuximab would present specific problems.
12. Are there any potential equality issues that should be taken into account when considering relapsed or refractory multiple myeloma and isatuximab with	People that have not responded well to proteasome inhibitors would obviously benefit from this treatment.

pomalidomide and dexamethasone? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	No

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- I have been treated by Isatuximab for two years as 4th line treatment and it has been the most effective treatment so far in controlling the disease as well as having no significant side effects.
- The result of this has not only been a good quality of life but has also positively impacted the lives of my family and enabled me through work and volunteering to contribute to the lives of a significant number of people which has been a major factor in enabling me to manage my mental health.
- The biggest challenge to mental and psychological well-being is the uncertainty about the future which is intensified as treatment options are reduced but is positively impacted by any increase by the addition of effective new treatment options.

Thank you for your time.

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Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma. [Review of TA658] A Single Technology Appraisal.

Produced by	Sheffield Centre for Health and Related Research (SCHARR), The University of Sheffield
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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.

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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. Kate Ren critiqued the statistical aspects of the submission. Matt Stevenson and Sunhong Kwon critiqued the health economic analysis submitted by the company and generated the EAG analyses. Dr Parrish and Dr Young provided clinical input. All authors were involved in drafting and commenting on the final report.

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Abbreviations

2K	Two knots
3K	Three knots
3L	Third-line
4L	Fourth-line
5L	Fifth-line
AE	Adverse event
AFT	Accelerated failure time
BIC	Bayesian Information Criterion
BNF	British National Formulary
BSA	Body surface area
CAS	Cancer Analysis System
CEAC	Cost-effectiveness acceptability curve
CDF	Cancer Drugs Fund
CS	Company's submission
CSR	Clinical Study Report
DSA	Deterministic sensitivity analysis
DVd	Daratumumab, bortezomib and low-dose dexamethasone
EAG	External Assessment Group
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
EQ-5D-3L	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
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
IPD	Individual patient data

IRC	Independent Response Committee
IRT	Interactive response technology
IsaPd	Isatuximab, pomalidomide and low-dose dexamethasone
IxaRd	Ixazomib, lenalidomide and dexamethasone
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
OS	Overall survival
PAS	Patient Access Scheme
Pd	Pomalidomide and low-dose dexamethasone
PFS	Progression-free survival
PH	Proportional hazards
PI	Proteasome inhibitor
PPS	Post-progression 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
SACT	Systemic anti-cancer treatment
SD	Standard deviation
STA	Single Technology Appraisal
TEAE	Treatment-emergent adverse event
TTD	Time to treatment discontinuation

1 EXECUTIVE SUMMARY

The company provided a submission to the National Institute for Health and Care Excellence (NICE) detailing the clinical-effectiveness of isatuximab, pomalidomide and low-dose dexamethasone (IsaPd) and the cost-effectiveness of IsaPd compared with pomalidomide and low-dose dexamethasone (Pd) and daratumumab monotherapy, with the latter comparison denoted exploratory. Incremental cost effectiveness ratios (ICERs) were provided expressed in terms of additional cost per additional quality-adjusted life years (QALYs) gained.

In a large deviation from standard NICE process, after factual accuracy check (AFC) the company provided a new base case analysis for the comparison with Pd that used entirely different clinical efficacy data (naïve comparison of Pd and IsaPd using real-world evidence) to that used in the submission which resulted in entry into the Cancer Drugs Fund, and which was used in the follow-up submission received by NICE in 2023 (data taken from the ICARIA-MM randomised controlled trial). For ease of readability, both company base cases are described with the latest described as 'base case AFC'; unless base case AFC is explicitly written all critique of the company's analyses relate to the original submission.

Section 1.1 provides an overview of the key issues identified by the External Assessment Group (EAG) in the comparisons of IsaPd with Pd and daratumumab monotherapy. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the incremental cost effectiveness ratio (ICER). Section 1.3 provides the EAG's base case ICER. These values presented in this report do not incorporate the commercial-in-confidence Patient Access Scheme (PAS) discounts for interventions other than isatuximab; the results which include these discounts are contained in a confidential appendix to this report. All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 provides a list of the EAG's key issues. These are issues that could make a large difference to the ICER; limitations identified that only make a small difference to the ICER are not included within the report.

Table 1: The EAG's key issues

Issue Number	Summary of issue	Report section
1	A perceived error identified within the company's model	4.3.2.1
2	The company used jointly-fitted lognormal distributions to model overall survival (OS) for the IsaPd and Pd comparison. This approach ensures that IsaPd would always have a benefit in OS. The EAG believes this is unlikely many years after progression on IsaPd treatment. The EAG instead used independently-fitted lognormal distributions which have been adjusted such that the risk of death for patients who received IsaPd is never higher than for Pd.	4.2.4.2.1 and 4.3.2.2
3	The company used jointly-fitted restricted cubic spline (RCS) Weibull distributions to mode progression-free survival (PFS) for the IsaPd and Pd comparison. The EAG preferred the use of independently-fitted lognormal distributions which has a lower Bayesian Information Criterion, an equally good visual fit to the data and does not require a constant treatment affect to be assumed.	4.2.4.2.2 and 4.3.2.3
4	The company did not cost the subsequent treatments that were used in the ICARIA-MM study which generated the survival data that were used to select survival distributions. When adjusting for impact of the subsequent therapies, the company's estimated OS after applying the two-stage estimation (TSE)-adjusted hazard ratio (HR) to account for subsequent daratumumab therapy lacks face validity. The EAG preferred applying the costs associated with these treatments to align costs and outcomes and not applying the TSE-adjusted HR.	4.3.2.4
5	The company preferred the use of a lognormal distribution to model OS for IsaPd and a Weibull distribution to model OS for daratumumab monotherapy in the comparison of IsaPd and daratumumab monotherapy. The EAG preferred the use of an RCS Weibull 3 knots distribution for IsaPd and the use of an RCS lognormal 2 knots model for daratumumab monotherapy.	4.2.4.3.1 and 4.3.2.5
6	The company used a model that allowed utility to vary in the PFS state based on the treatment that is used. The EAG has explored the impact of using a model where the utility in the PFS was independent of treatment.	4.3.2.6
7	The company's assumed an administration cost of £281.11 for every subcutaneous injection. The EAG only used this cost for the first dose.	4.2.4.6.1 and 4.3.2.7
8	The company used the mean weight for all patients in its base case. The EAG prefers to use a distribution which decreases the cost of isatuximab.	4.2.4.6.1 and 4.3.2.8
9	The company relied on a naïve indirect treatment comparison to estimate the relative efficacy of IsaPd and daratumumab monotherapy.	3.4.2 and 4.3.2.9
10	The company relied on a naïve indirect treatment comparison to estimate the relative efficacy of IsaPd versus Pd in its base case AFC.	3.4.3 and 4.3.2.10
11	The EAG believes that alternative distributions are more appropriate to model OS in the IsaPd versus Pd comparison in the company's base case AFC.	4.3.2.11

1.2 Overview of key model outcomes

NICE technology appraisals estimate how much a new technology changes the length of life and the quality of life using the change in QALYs.

The company's model assumes that IsaPd affects QALYs by:

- Prolonging overall survival (OS)
- Prolonging the time that a patient stays in the progression-free survival (PFS) health state which has a higher utility than the progressed disease health state
- Having a higher utility for the PFS health state for patients receiving IsaPd than for patients receiving Pd or daratumumab monotherapy.

The company's model assumes that IsaPd costs by:

- The inclusion of the acquisition costs of isatuximab
- Reducing the discounted costs associated with death due to survival being extended
- Reducing the costs of subsequent treatments compared with daratumumab monotherapy
- An increase in the costs of adverse events.

1.3 The decision problem: summary of the EAG's key issues

The EAG has no key issues with the decision problem.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG notes that the comparison of IsaPd and daratumumab monotherapy was a naïve indirect comparison which will be at risk of bias. Whilst the EAG acknowledges the reason for such an approach this will lead to uncertainty in the relative efficacy estimate (see Issue 6 in Section 1.1). The company's base case AFC changed to a naïve indirect comparison between IsaPd and Pd about which the EAG had strong reservations due to potential bias that could be caused by unreported differences in the patient population.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

The EAG preferred alternative distributions to model OS in both the comparisons of IsaPd and Pd, both initial submission and AFC, and of IsaPd and daratumumab monotherapy (Issues 2, 5 and 11 in Section 1.1). The EAG preferred alternative distributions to model PFS in the IsaPd and Pd comparison (Issue 3 in Section 1.1). The EAG preferred to include the costs of the treatments used in the ICARIA-MM study that were associated with observed survival (Issue 4 in Section 1.1). The EAG also noted potential uncertainty in whether utility in the PFS health state was treatment-dependent (Issue 6 in Section 1.1);

this assumption had a relatively large impact on the ICER. The perceived error within the company's model (Issue 1 in Section 1.1) had a relatively large impact on the ICER, but the directional change when interacting with other changes, differed on whether the company's initial base case or the base case AFC was used.

1.6 Other key issues: summary of the EAG's view

The EAG has no other key issues.

1.7 Summary of EAG's preferred assumptions and resulting ICERs

Section 1.7.1 compares IsaPd with Pd (original submission); Section 1.7.2 compares IsaPd with Pd (AFC); Section 1.7.3 compares IsaPd with daratumumab monotherapy.

1.7.1 Comparison of IsaPd with Pd (original submission)

The EAG's preferred assumptions are:

- The correction of the perceived modelling error
- The use of independently-fitted lognormal distributions to model PFS in the IsaPd versus Pd comparison
- Incorporating the costs of subsequent treatments observed in the ICARIA-MM study for the comparison of IsaPd versus Pd
- Using a distribution for weight rather than assume all patients have the mean value

The modelling assumptions that have the greatest effect on the company's base case ICER are related to the choice of distributions to model OS, whether utility in a health state is dependent on treatment and whether the costs associated with treatments provided in the ICARIA-MM study are included in the model.

Table 2 summarises the results of the EAG's exploratory analysis for the comparison of IsaPd and Pd. The EAG's base case ICER is estimated to be £264,785 (deterministic) and noticeably lower at £225,430 (probabilistic) - result not shown in Table 2 - assuming a disease severity modifier of 1.0.

The company made a claim for a QALY weighting above 1 to be applied in the comparison with Pd, based on the QALY weighting for daratumumab and stating that Pd should have worse efficacy than daratumumab monotherapy. The EAG generates the same severity modifiers as the company but notes that the populations in the two comparisons (versus Pd and daratumumab monotherapy) are different, with the population for Pd coming from the ICARIA-MM study, whereas the population for daratumumab monotherapy is drawn from patients whose data has been included in the systemic anti-cancer treatment dataset. The EAG comments that if patients in ICARIA-MM had poorer prognosis (as

may be seen in patients treated in the real world) than observed, then it is likely that the additional QALYs gained due to the use of IsaPd would also be lower than modelled when using ICARIA-MM data. The EAG therefore prefers to use a disease severity modifier of 1.0 but has provided results when a severity modifier of 1.2 was assumed.

Table 2: The EAG's deterministic base case: IsaPd versus Pd

Scenario	Incremental cost (£)	Incremental QALYs	Cost per QALY (£)	
			Severity modifier of 1.0*	Severity modifier of 1.2
Company's base case after the clarification process	[redacted]	[redacted]	182,769	152,307
EA1: Correction of the perceived error	[redacted]	[redacted]	190,183	158,486
EA2: Use of independently fitted lognormal distributions for OS but constraining so that the risk in the IsaPd arm was never greater than in the Pd arm	[redacted]	[redacted]	248,450	207,042
EA3: Use of independently-fitted lognormal distributions for PFS	[redacted]	[redacted]	186,221	155,184
EA4: Costs of subsequent treatments set to that observed in ICARIA-MM	[redacted]	[redacted]	203,070	169,225
EA5: Using the distribution of weight rather than the mean weight	[redacted]	[redacted]	181,577	151,314
EAG base case (EA1-EA5 combined)	[redacted]	[redacted]	264,785	220,654

LYG - life year gained; QALY - quality-adjusted life year
** The EAG prefers to use a disease severity modifier of 1.0*

Table 3 provides scenario analyses starting from the EAG's base case exploring uncertainties relating to different distributions used to model OS and PFS and assuming that utility in a health state was independent of treatment.

Table 3: Deterministic ICERs from scenario analyses starting from the EAG's deterministic base case results: IsaPd versus Pd

Scenario	Incremental cost (£)	Incremental QALYs	Cost per QALY (£)	
			Severity modifier of 1.0*	Severity modifier of 1.2
EAG base case (deterministic)	[redacted]	[redacted]	264,785	220,654
SA1a: Use of jointly-fitted lognormal distributions for OS	[redacted]	[redacted]	193,389	161,158
SA1b: Use of exponential distributions for OS	[redacted]	[redacted]	249,891	208,243
SA2: Use of a jointly-fitted RCS Weibull model for PFS	[redacted]	[redacted]	258,081	215,067
SA3: Assuming that utility in a health state were independent of treatment	[redacted]	[redacted]	307,844	256,537

LYG - life year gained; QALY - quality-adjusted life year
** The EAG prefers to use a disease severity modifier of 1.0*

These scenarios resulted in deterministic ICERs ranging from £193,389 to £307,844 assuming a disease severity modifier of 1.0. The lower value is when the company's preferred choice for modelling OS is used; the upper value is when it is assumed that the utility in PFS is equal for patients receiving IsaPd and Pd.

1.7.2 Comparison of IsaPd with Pd (AFC)

The EAG's preferred assumptions are:

- The correction of the perceived modelling error
- The use of an RCS Weibull 3 knots distribution to model OS for IsaPd and the use of an RCS Weibull with 1 knot distribution to model OS for Pd
- Using a distribution for weight rather than assume all patients have the mean value

The modelling assumption that had the greatest effect on the company's base case ICER was related to the choice of distributions to model OS.

Table 4 summarises the results of the EAG's exploratory analysis for the comparison of IsaPd and Pd. The EAG's base case ICER is estimated to be £132,606 (deterministic) and £129,663 (probabilistic) assuming a disease severity modifier of 1.2.

Table 4: The EAG's deterministic base case: IsaPd versus Pd AFC

Scenario	Incremental cost (£)	Incremental QALYs	Cost per QALY (£)	
			Severity modifier of 1.0	Severity modifier of 1.2*
Company's base case after the clarification process	[redacted]	[redacted]	124,744	103,953
EA6: Correction of the perceived error	[redacted]	[redacted]	130,379	108,649
EA7: Use of an RCS Weibull with 3 knots for IsaPd and an RCS Weibull with 1 knot for Pd	[redacted]	[redacted]	153,182	127,652
EA8: Using the distribution of weight rather than the mean weight	[redacted]	[redacted]	124,034	103,362
EAG base case (EA6, EA7 and EA8 combined)	[redacted]	[redacted]	159,127	132,606

LYG - life year gained; QALY - quality-adjusted life year
** The EAG prefers to use a disease severity modifier of 1.2*

Table 5 provides scenario analyses starting from the EAG's base case exploring uncertainties relating to different distributions used to model OS and assuming that utility in a health state was independent of treatment.

Table 5: Deterministic ICERs from scenario analyses starting from the EAG's deterministic base case results: IsaPd versus Pd AFC

Scenario	Incremental cost (£)	Incremental QALYs	Cost per QALY (£)	
			Severity modifier of 1.0*	Severity modifier of 1.2
EAG base case (deterministic)	[redacted]	[redacted]	159,127	132,606
SA4a: Use of a lognormal distributions for OS for IsaPd	[redacted]	[redacted]	126,612	105,510
SA4b: Use of a lognormal distributions for OS for Pd	[redacted]	[redacted]	165,091	137,576
SA5: Assuming that utility in a health state were independent of treatment	[redacted]	[redacted]	165,514	137,928

LYG - life year gained; QALY - quality-adjusted life year
** The EAG prefers to use a disease severity modifier of 1.0*

These scenarios resulted in deterministic ICERs ranging from £126,612 to £165,514 assuming a disease severity modifier of 1.0. The lower value is when the company's preferred choice for modelling OS is

used; the upper value is when it is assumed that the utility in PFS is equal for patients receiving IsaPd and Pd.

1.7.3 Comparison of IsaPd with daratumumab monotherapy

The EAG's preferred assumptions are:

- The correction of the perceived modelling error
- The use of an RCS Weibull 3 knots distribution for IsaPd and the use of an RCS lognormal 2 knots model for daratumumab monotherapy.
- Assuming no administrative costs for subcutaneous injections after the first dose
- Using a distribution for weight rather than assume all patients have the mean value

Table 6 summarises the results of the EAG's exploratory analysis for the comparison of IsaPd and daratumumab monotherapy. The EAG's base case ICER is estimated to be £323,799 (deterministic) assuming a severity modifier of 1.2; the model could not be run probabilistically for the EAG base case although the probabilistic ICER is anticipated to be similar to the deterministic estimate as in the company's base case the probabilistic ICER was 2% higher than the deterministic ICER.

Table 6: The EAG's deterministic base case: IsaPd versus daratumumab monotherapy

Scenario	Incremental cost (£)	Incremental QALYs	Cost per QALY (£)	
			Severity modifier of 1.0	Severity modifier of 1.2*
Company's base case after the clarification process	[redacted]	[redacted]	141,251	117,709
EA9: Correction of the perceived error	[redacted]	[redacted]	149,397	124,497
EA10: Alternative distributions for OS (RCS Weibull with 3 knots for IsaPd and an RCS lognormal with 2 knots for daratumumab monotherapy)	[redacted]	[redacted]	358,144	298,454
EA11: Assuming no administration costs after the first dose for subcutaneous injections	[redacted]	[redacted]	145,884	121,570
EA12: Using the distribution of weight rather than the mean weight	[redacted]	[redacted]	140,217	116,848
EAG base case (EA7, EA8 and EA9 combined)	[redacted]	[redacted]	388,559	323,799

LYG - life year gained; QALY - quality-adjusted life year
** The EAG prefers to use a disease severity modifier of 1.2**

Table 7 provides scenario analyses starting from the EAG's base case exploring uncertainties relating to different distributions used to model OS and assuming that utility in a health state was independent of treatment.

Table 7: Deterministic ICERs from scenario analyses starting from the EAG's deterministic base case results: IsaPd versus daratumumab monotherapy

Scenario	Incremental cost (£)	Incremental QALYs	Cost per QALY (£)	
			Severity modifier of 1.0	Severity modifier of 1.2*
EAG base case (deterministic)	[redacted]	[redacted]	388,559	323,799
SA6a: Assuming a lognormal distribution for OS for IsaPd	[redacted]	[redacted]	200,521	167,100
SA6b: Assuming a Weibull distribution for OS for daratumumab monotherapy	[redacted]	[redacted]	240,414	200,345
SA7: Assuming that utility in a health state were independent of treatment	[redacted]	[redacted]	448,141	373,451

LYG - life year gained; QALY - quality-adjusted life year
** Numbers in parentheses are ICERs assuming a disease severity model of 1.2*

These scenarios resulted in deterministic ICERs ranging from £167,100 to £373,451 assuming a disease severity modifier of 1.2. The lower value is when the company's preferred choice for modelling OS is used; the upper value is when it is assumed that the utility in PFS is equal for patients receiving IsaPd and daratumumab monotherapy.

2 BACKGROUND

This document critiques the company submission (CS)[1] for isatuximab, pomalidomide and low-dose dexamethasone (IsaPd) following exit from the Cancer Drugs Fund (CDF). Prior to this, a previous CS[2] and External Assessment Group (EAG) report[3] informed a NICE Final Appraisal Determination.[4]

The CS was originally sent to the EAG in April 2023, but then the STA was suspended, before being reactivated in September 2023. The EAG has already formally critiqued large parts of the previous CS[1] and the accompanying economic model that are retained in the most recent CS.[2] The most notable changes between the two CSs is that the data from the key study (ICARIA-MM) are now considerably more mature and that a new comparator has been added to the decision problem as daratumumab monotherapy has been approved by NICE in the interim.[5]

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.[6] 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.[7] 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 CS.[1]

2.2 Critique of company's overview of current service provision

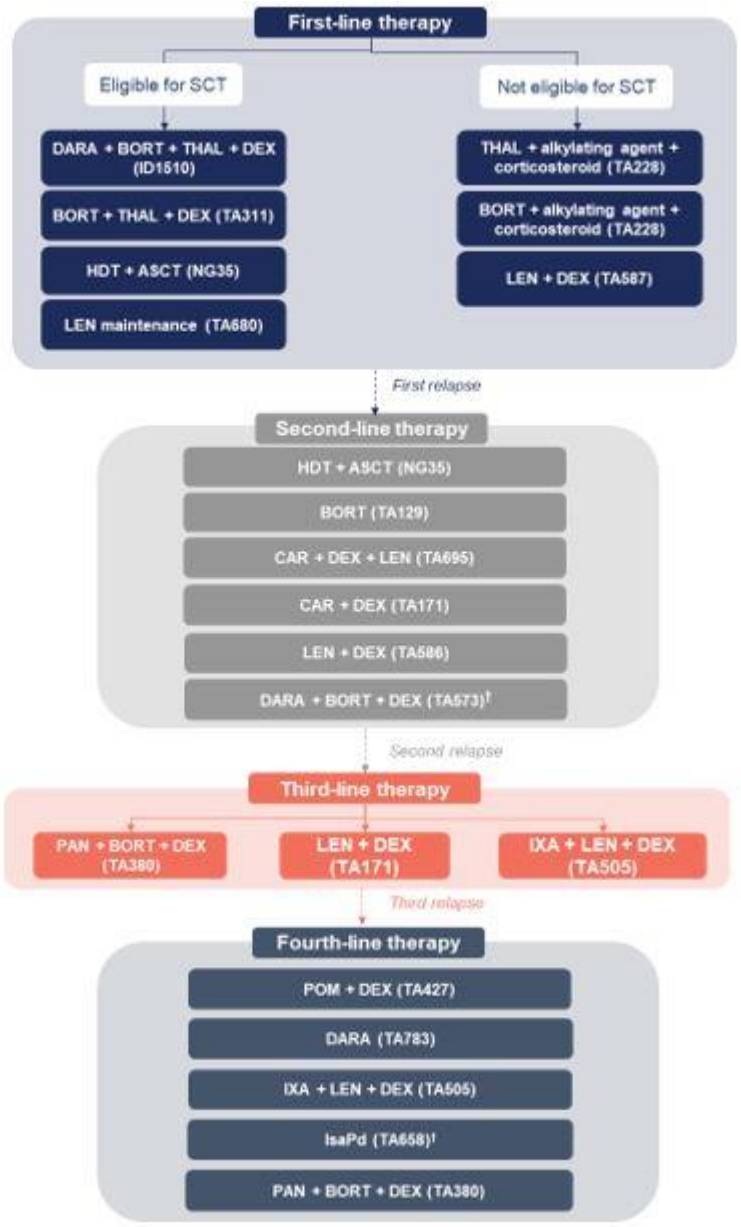
The CS[1] describes the clinical pathway for treating patients with MM and also indicates the proposed positioning of IsaPd (reproduced as Figure 1). IsaPd was recommended in the CDF as a fourth-line (4L) treatment and this is the positioning explored in the new CS. Treatments routinely recommended by NICE at 4L and included within the final scope[8] are: pomalidomide and dexamethasone (Pd); daratumumab monotherapy; and ixazomib and lenalidomide and dexamethasone (IxaRd).

As stated by the company and supported in clinical advice provided to the EAG in the future it is anticipated that the proportion of patients eligible for IsaPd is likely to decline due to the use of daratumumab in combination with bortezomib, thalidomide and dexamethasone at first line and the use of daratumumab, bortezomib and dexamethasone at second-line as patients who are refractory to an anti-CD38 agent were excluded from the ICARIA-MM randomised controlled trial (RCT).[9]

After the company had submitted the CS, NICE approved the use of daratumumab, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable; this could also reduce the use of IsaPd. 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 in between.

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] and lead team presentation for daratumumab monotherapy CDF review of TA520. †Note that this represents therapies that are available in the cancer drugs fund.

Abbreviations: ASCT, autologous stem cell transplant; BORT, bortezomib; CAR, carfilzomib; CDF, Cancer Drugs Fund; DARA, daratumumab monotherapy; DEX, dexamethasone; HDT, high-dose therapy; IXA, ixazomib; LEN, lenalidomide; MM, multiple myeloma; NG, NICE guidance; NICE, National Institute for Health and Care Excellence; PAN, panobinostat; POM, pomalidomide; SCT, stem cell transplant; TA, technology appraisal; THAL, thalidomide.

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[8] in that the company have restricted IsaPd use to those at 4L.

2.3.2 Intervention

The intervention described in the CS is consistent with the final NICE scope,[8] which is the use of isatuximab, a humanised monoclonal antibody which binds to cell surface glycoprotein CD38, in combination with pomalidomide and dexamethasone. IsaPd received European Medicines Agency (EMA) marketing authorisation in May 2020. Isatuximab is indicated in combination with pomalidomide and dexamethasone, for the treatment of adult patients with RRMM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) (bortezomib, carfilzomib or ixazomib) and have demonstrated disease progression on the last therapy. This is the relevant indication for this STA.

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 (IV) 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[8] are Pd, daratumumab monotherapy and IxaRd plus three interventions that are subject to NICE evaluation (elranatamab, ciltacabtagene autoleucel and belantamab mafodotin). None of the interventions subject to NICE evaluation have had guidance published as of the 19th of September 2023, with a decision on elranatamab anticipated in February,[10] the STA of ciltacabtagene autoleucel,[11] and the manufacturers of belantamab mafodotin having appealed the NICE guidance.[12] In addition, the company has stated that patients eligible for treatment with IsaPd would not receive any of these three interventions.

The company's base case focusses on Pd and daratumumab monotherapy as comparators although the comparison with daratumumab monotherapy is marked exploratory. IxaRd was not considered a comparator by the company as IsaPd is indicated in a population that has had at least two lines of therapy including lenalidomide whereas IxaRd includes lenalidomide and would be prescribed to patients that are not refractory to lenalidomide.

For Pd, 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 IV or orally, is provided on days 1, 8, 15 and 22 of each 28-day cycle.

Daratumumab monotherapy was assumed to be administered subcutaneously as follows: 16 mg/kg infusion on days 1, 8, 15 and 22 of each four-week cycle in cycles 1 and 2, then on days 1 and 15 of each four-week cycle in cycles 3–6, then day 1 of each four-week cycle thereafter.

2.3.4 Outcomes

The outcomes in the CS are in line with those in the final scope issued by NICE.[8]

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 daratumumab, which are direct comparators at 4L, also have agreed simple PAS discounts in place; however, these are commercial-in-confidence. 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.

[redacted]

3 CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the clinical effectiveness evidence contained within the CS[2] 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 EAG. 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 updated CS and updated CS Appendix D.[1]

3.1.1 Searches

The company performed a systematic literature review to identify all clinical effectiveness and safety studies of isatuximab or comparator treatments for adult patients who have relapsed and refractory multiple myeloma. The original search was first conducted in October 2018, followed by two reported updates in June 2019 and November 2022.

A clarification question concerning the clinical effectiveness searches was raised with the company (clarification letter A3, page 3) to confirm that no new and relevant studies have been published since the last updated search (database searches in November 2022 and hand searching in December 2022). In response, and as of October 2023, the company has undertaken a pragmatic and partial update of the systematic literature review (SLR) search (company response A3, pages 5-8) of electronic database search, clinical trial registry, and HTA agency search. While the number of records from the update search and updated PRISMA diagram was not provided, the company concluded that they did not expect any new and relevant clinical evidence to be found.

The company searched several electronic bibliographic databases (Appendix D.1: Identification and Selection of Relevant Studies): MEDLINE, including MEDLINE in Process (via Ovid), EMBASE (via Ovid), Cochrane Central Register of Controlled Trials (via Wiley), Cochrane Database of Systematic Reviews (via Wiley), Database of Abstracts of Reviews of Effects (via CRD), and Health Technology Assessment database (via CRD). The company hand-searched the bibliographies of relevant systematic reviews and network meta-analyses to identify other new studies for inclusion.

Handsearching included the clinicaltrials.gov registry and WHO International Clinical Trials Registry Platform for ongoing, completed, or unpublished trials (up to October 2023). The company also searched several key conference abstract websites (up to December 2022): the American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH), the European Hematology Association (EHA), the European Society of Hematology (ESH), and the European Society for Medical Oncology (ESMO). The terms applied and numbers retrieved in the search were fully reported (in all three searches). Six health technology assessment agencies (up to December 2022): the National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Institute for Clinical and Economic Review, the Pharmaceutical Benefits Advisory Committee (PBAC), and the Haute Autorité de Santé (HAS).

Two additional grey literature sources were searched: Drugs@FDA and the European Medicines Agency (up to December 2022). The company also searched the clinical study reports in both the de novo and SLR updates.

The company acknowledged that the de novo SLR search was broad (CS B.2.1 Identification and Selection of Relevant Studies, page 35) and that a range of interventions included were not within the NICE scope (bendamustine, carfilzomib, elotuzumab, ixazomib, lenalidomide, melphalan, thalidomide, and vorinostat) compared to the update search, which only included the relevant interventions and comparators (isatuximab, bortezomib, daratumumab, dexamethasone, panobinostat, and pomalidomide). It was unclear to the EAG, the purpose of modifying the original RCT filter from the Scottish Intercollegiate Guidelines Network and the impact on the sensitivity of the search. In addition, it was unclear why the RCT filter in the Embase and MEDLINE de novo search (Appendix D.1.4.1.1, pages 21–25) differed from the update search (Appendix D.1.4.1.2, pages 32–36).

Except for the company clarification response, the reported searches in the CS are transparent and fully reported (provision of full search strategies and detailed PRISMA diagrams) in both database and supplementary and grey literature searches. Overall, the EAG considered that the company search was comprehensive and that there were no observable and/or consequential errors in the search approach and strategies.

3.1.2 Inclusion criteria

The inclusion criteria for the 2022 clinical SLR update are generally consistent with the NICE final scope,[8] 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 PI in a prior line of treatment; (2) the final NICE scope specifies ixazomib in combination with lenolidomide and dexamethasone

(subject to NICE evaluation) for people who have had two previous therapies, daratumumab monotherapy and ixazomib in combination with lenolidomide and dexamethasone (subject to NICE evaluation) for people who have had three previous therapies, pomalidomide in combination with low-dose dexamethasone, elranatamab (subject to NICE evaluation) and ciltacabtagene autoleucel (subject to NICE evaluation) for people who have had three or more previous therapies, and belantamab mafodotin (subject to NICE evaluation) for people who have had four previous therapies, whereas the company's systematic review inclusion criteria lists only IsaPd, PanVd, Pd and daratumumab monotherapy (and CS Appendix D specifies that only IsaPd, Pd and daratumumab monotherapy were relevant to the NICE decision problem for this appraisal. While not consistent with the stated decision problem, the EAG does not consider these differences to be problematic, as (1) would broaden rather than narrow the scope of the review, meaning that the relevant papers would still have been identified, and (2) refers to treatments that have not yet been evaluated and / or recommended by NICE. 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 EAG 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 updated CS[1] states that two reviewers independently undertook record selection, with a third reviewer adjudicating any disagreements, and that two reviewers also undertook full text screening, with arbitration provided by a third, more senior, reviewer. The EAG considers these to be appropriate and high-quality reviewing methods. Neither the EAG nor clinical advisors to the EAG are aware of any additional studies within the scope of this appraisal.

The PRISMA flow diagram for both the *de novo* and update SLRs (Figure 3, CS, Appendix D)[1] refers to a total of seven studies identified that were considered of relevance to the submission, five of which were presented as being publications identified through the *de novo* and update SLRs and three of which were presented as being from unpublished data. In response to clarification question A1, the company stated that data from ICARIA-MM was included in both the five unique studies identified through the *de novo* and update SLRs, and the three studies from unpublished data, and therefore that the total list of seven unique studies considered relevant to the decision problem consists of ICARIA-MM, SIRIUS, COLUMBA, NCT02477891, REBUILD, systemic anti-cancer treatment (SACT) data for IsaPd and SACT data for daratumumab monotherapy.[13] In response to clarification question A3, the company provided a further update to the SLR from October 2022 to October 2023, and stated that seven unique studies were identified in this most recent update: APOLLO, ELOQUENT-3, ICARIA-MM, and OCEAN, CHECKMATE 602, LIGHTHOUSE and CGRP-MM, of which only ICARIA-MM (already

included in the SLR and submission) was the only study to examine IsaPd, and APOLLO and LIGHTHOUSE were the only studies to examine daratumumab monotherapy.[13]

3.1.4 Critique of data extraction

No detail is reported in the CS[13] about the process of data extraction for the updated SLR, 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.

3.1.5 Critique of quality assessment

The study quality of the ICARIA-MM RCT[9] 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,[14] which is widely regarded as the most robust tool for the assessment of bias in RCTs. Risk of bias was assessed by single reviewer checked by a second reviewer. The method for resolving disagreements was not reported. The EAG considers this to be a less robust reviewing method than assessment of risk of bias by two independent reviewers with adjudication by a third reviewer where needed to resolve disagreements.

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.[1]

Quality assessment of the included study, ICARIA-MM, as undertaken by the company and the EAG, is presented in Section 3.2.3. The quality assessment for the SIRIUS study has not been undertaken in this appraisal as this study (known at that time as MMY2002) was the key study in the daratumumab appraisal[5] and had therefore been seen as acceptable quality by NICE. In brief, SIRIUS was a single arm, phase II study investigating different doses of daratumumab with 106 patients recruited.

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[2] 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.[9] 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.[2, 15] 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.[2]

ICARIA-MM is used in the model for the comparison of IsaPd and Pd, and comparison of SACT data for both isatuximab and daratumumab monotherapy was used for the comparison of IsaPd and daratumumab monotherapy (see Section 3.4).

3.2.1.1 Patients

Eligibility criteria for the ICARIA-MM study are presented in Tables 6 and 7 of the CS,[2] pages 32 to 38. One key difference between the eligibility criteria for the ICARIA-MM study and the NICE final scope[16] is that patients were excluded from the ICARIA-MM study[9] if they had been treated with anti-CD38 monoclonal antibody and were refractory to this treatment. As such, 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 EAG 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, (such patients will typically have received a non-anti-CD38-based treatment in between).

A flow diagram of patient flow through the ICARIA-MM study is presented in Figure 3, page 48 of the CS,[2] 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).[15] 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.[2] 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 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.[2]

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 46 to 49): there was a greater proportion of patients aged ≥65 years in the IsaPd than the Pd arm (64.9% versus 54.2%, respectively; 63.5% versus 53.4% respectively in the 4L population); a greater proportion of males in the IsaPd than the Pd arm (57.8% versus 45.8%, respectively; 57.7% versus 46.6% respectively in the 4L population); and fewer patients from Western Europe in the IsaPd than the Pd arm (35.7% versus 49.7%, respectively; 36.5% versus 50.0% respectively in the 4L population), with a greater proportion of patients from Eastern Europe (18.2% versus 13.1%, respectively; 25.0% versus 17.2% respectively in the 4L population) and Asia (13.6% versus 9.8%, respectively; 9.6% versus 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% versus 33.8%, respectively; 40.4% versus 37.5% respectively in the 4L population). Clinical advice received by the EAG 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% versus 23.5%, respectively; 15.4% versus 22.4% respectively in the 4L population); del(17p) and t(4;14) were the most frequent abnormalities. Clinical advice received by the EAG 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,[2] the EAG 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% versus 45.1%, respectively; 40.4% versus 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% versus 44.4%, respectively; 48.1% versus 39.7% respectively in the 4L population), which may have been unfavourable to IsaPd.

The EAG 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 EAG 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 EAG 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 EAG 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).[2] Permitted and disallowed concomitant treatments are detailed in the CS, Table 6, page 33. The company's clarification response to question A4[15] 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.

The total number of protocol deviations that were not due to the COVID-19 pandemic considered to be '*critical or major*' was not reported in the CSR.[17] 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 EAG considers this to be an appropriate comparator.[18] Permitted and disallowed concomitant treatments were the same as for the IsaPd arm, and are detailed in the CS, Table 6, page 33.[2] The company's clarification response to question A4[15] 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

Clinical effectiveness data for the following outcomes were reported in the CS:

- 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
- Overall survival (OS) – time from the date of randomisation to the date of death from any cause
- Time to definitive treatment discontinuation
- Time to subsequent treatments
- Health-related quality of life (HRQoL)

Some outcomes mentioned in the final NICE scope[8] were not included in the CS. All efficacy and HRQoL outcome data from ICARIA-MM were analysed *post hoc* within the 4L population, as IsaPd is currently recommended as a 4L treatment for RRMM.

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.[2] 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.[18] For the current appraisal, PFS data from the final analysis cut-off date (14th March 2022) were used. 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.[15]

Secondary outcomes

Outcomes listed in the final NICE scope[16] and reported in the CS[2] as secondary outcomes included:

- Overall survival (OS)
- Time to definitive treatment discontinuation
- Time to subsequent treatments
- HRQoL
- Adverse events

Along with PFS, these outcomes form the focus of this report. Data on other outcomes are presented in the CS.[2]

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.[18]

Time to definitive treatment discontinuation and time to subsequent treatments might be considered among the "*alternative endpoints*" suggested by the EMA research recommendations[18] as acceptable.

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 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 EAG, 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 and in the reference pack for ID4067 Review submission.[15] Clinical advice received by the EAG suggested that the global health status 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[18] and EMA guidance on measuring HRQoL in oncology[19] 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.[2] These were defined as AEs that "*developed, worsened (according to the investigator opinion) or became serious during the TEAE period*" (interim CSR, page 44).[15] The method of measuring AEs was not given in the CS,[2] although the interim CSR (page 44)[15] reported that all AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. According to the initial CS (page 46),[2] 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.[2] In response to clarification question A15, the company stated that safety data relating to the 4L sub-population was from the ITT safety population.[13] No definition of what

constituted a serious adverse event (SAE) is presented in the CS[1, 2] or CSR.[20] 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*".[21]

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 versus ≥75 years) and number of previous lines of therapy (2 or 3 versus >3) (CS, page 48).[1] The EAG considers that the study design could have been more rigorous, as the ICARIA-MM trial was open-label and the EMA evaluation guidelines[18] 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,[2] and the updated CS focuses on the 4L subgroup.[1] The EAG'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 EAG 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.[22] 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 EAG is not aware of any ongoing studies examining the effectiveness of IsaPd.

3.2.2 Details of relevant studies not included in the submission

The EAG is confident that the ICARIA-MM study is the only relevant study in this patient population, and that no relevant studies have been omitted from the CS.[1] 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[9] using the checklist recommended by NICE, which bears a close resemblance to the Cochrane Risk of Bias tool.[23] A summary of the risk of bias in the ICARIA-MM study undertaken by the company alongside the EAG's independent quality assessment is presented in Table 8. The EAG has also specified the level of risk of bias for each criterion.

The company's critical appraisal and the EAG's critical appraisal of the ICARIA-MM study[9] were similar. The EAG 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 EAG 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 (updated CSR, Table 4, page 44).[17] The EAG urges caution in applying this critical appraisal to the 4L data presented in the current submission, however, as the 4L sub-population represents a *post-hoc* analysis (see Section 3.2.4.7 and Section 3.6.3).

Table 8: Company and EAG quality assessment of ICARIA-MM (adapted from CS, Appendix K, Table 46)

Quality assessment criterion question	Company quality assessment (yes/no/not clear/NA)		EAG 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% versus 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[17] does not report the total number of critical or major protocol deviations that were not due to the COVID-19 pandemic in the IsaPd arm and the Pd arm. Slightly more patients in the IsaPd arm ([redacted]) than in the Pd arm ([redacted]) had critical or major protocol deviations relating to assessments/procedures, a similar proportion in the Isa Pd ([redacted]) and Pd ([redacted]) arms had critical or major protocol deviations relating to clinical safety, slightly more patients in the Pd arm ([redacted]) than the IsaPd arm ([redacted]) had critical or major protocol deviations relating to concomitant medications/therapy, slightly more patients in the IsaPd arm ([redacted]) than the Pd arm ([redacted]) had critical or major protocol deviations relating to IMP management, [redacted] patients in the Pd arm ([redacted]) had critical or major protocol deviations relating to informed consent procedures (but [redacted] in the IsaPd arm), and [redacted] in each arm ([redacted] and [redacted] in the IsaPd and Pd arms, respectively) had critical or major protocol deviations relating to source data records, and other critical or major protocol deviations. The EAG 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 median relative dose intensity (RDI) of pomalidomide was [redacted] in the IsaPd arm, and [redacted] in the Pd arm (CSR, page 60).[17] 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.

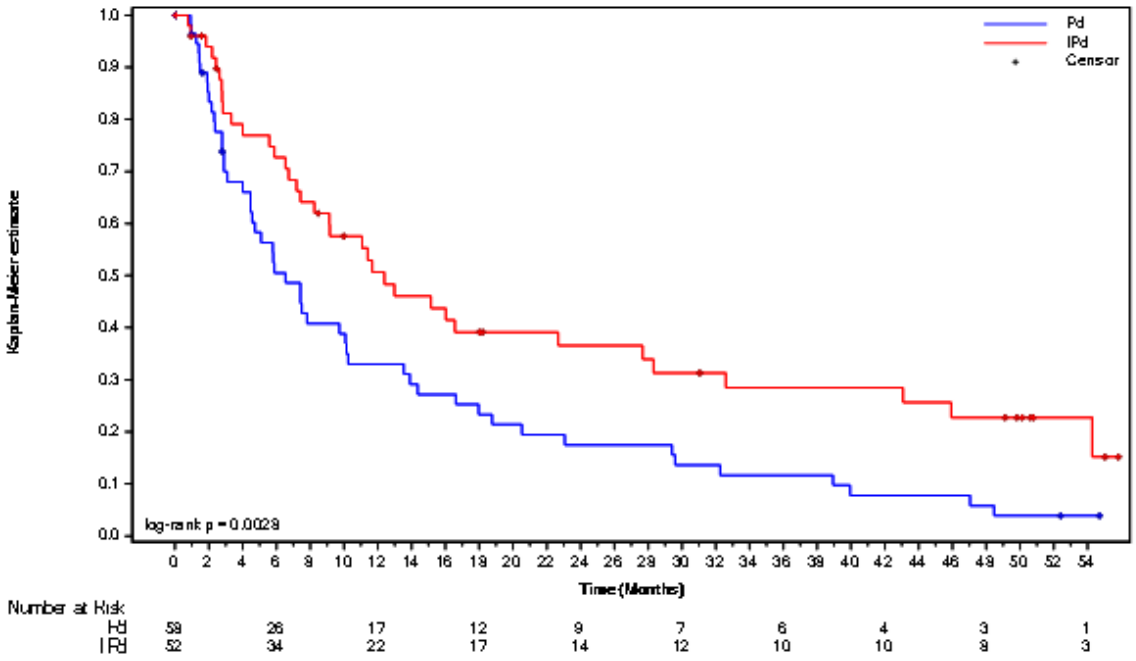
3.2.4 Summary and critique of results

The data cut-off date for the efficacy analyses was the 14th of March 2022, and the cut-off date for OS was the 27th of January 2022, which represents the final analysis; this incudes data for the 4th line subgroup.[1] The mean (SD) duration of exposure was [redacted] ([redacted]) and [redacted] ([redacted]) weeks for the IsaPd and Pd arms, respectively, and the median (range) duration of exposure was [redacted] and [redacted] weeks for the IsaPd and Pd arms, respectively.[17]

3.2.4.1 PFS (primary endpoint)

In the 4L population, at the final analysis, the median PFS was greater in the IsaPd arm (12.39 months [95% CI: 7.425, 27.663]) than in the Pd arm (6.54 [95% CI: 4.468, 10.086]) (stratified by age; *p*-value versus Pd: 0.0057), and the stratified (by age) hazard ratio (HR) was 0.536 (95%: CI 0.343, 0.840), which the CS states represents a 46.4% risk reduction of disease progression or death in favour of IsaPd compared with Pd (Figure 2).[1]

Figure 2: Kaplan-Meier curves for PFS by treatment group, 4L population (reproduced from CS, Figure 4, page 60)



Source: Sanofi, Clinical study report fourth-line analysis, data on file (2022) (87), cut-off date: 14th March 2022.
Notes: Log-rank p value: Stratified on age (<75 years versus >=75 years) according to IRT. One-sided significance level is 0.025.
IsaPd - isatuximab + pomalidomide + dexamethasone; Pd - pomalidomide + dexamethasone; PFS - progression-free survival.

3.2.4.2 OS

In the 4L population of ICARIA-MM, there were 74 death events; 32 (61.5%) in the IsaPd arm and 42 (72.4%) in the Pd arm at data cut-off date for the final analysis for OS (27th of January 2022); 38.5% of 4L patients in the IsaPd arm and 27.6% of 4L patients in the Pd arm were censored at the final cut-off date. Greater median OS in the IsaPd arm (compared with the Pd arm) was reported in the CS, with a median OS of 33.28 months (95% CI :18.431, 54.275) in the Isa Pd arm and a median OS of 17.71 months (95% CI: 11.565, 27.532) in the Pd arm (stratified HR 0.657 [95% CI 0.409, 1.055], *p*=0.080) (Figure 3; CS, pages 60-61).[1]

OS may have been impacted by the subsequent use of daratumumab which does not reflect current clinical pathways in England. The CS[1] reported that eight (18.2%) and 23 (41.1%) 4L patients in the IsaPd and Pd arms, respectively, had received daratumumab as subsequent therapy at the cut-off date for the final analysis. 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 National Health Service (NHS) in England. The CS presents sensitivity analyses adjusting the ICARIA-MM OS data using inverse probability of censoring weighting (IPCW)

and two-stage estimation (TSE) to account for subsequent daratumumab therapy. The company concludes that subsequent daratumumab therapy does not appear to impact the relative treatment effect of IsaPd versus Pd (see results reproduced in Table 9), however the company urges caution in interpreting these analyses given the small sample size and the assumptions required to be made.[1]

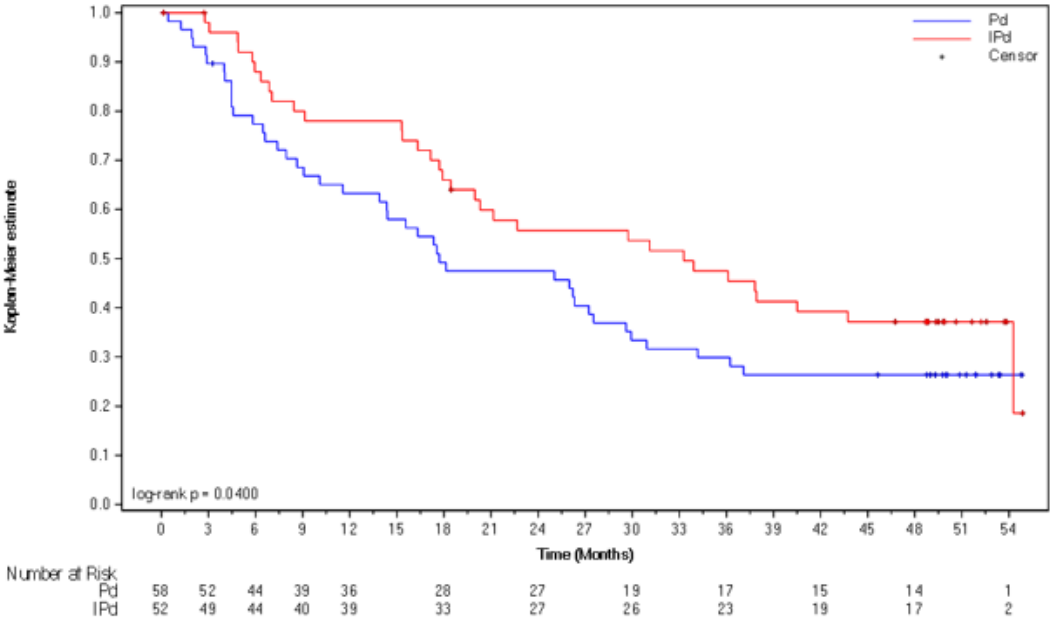
Table 9: ICARIA-MM secondary efficacy outcome – OS†– sensitivity analyses by further therapy with daratumumab, 4th line population (reproduced from Table 16 of CS)

Analysis	IsaPd versus Pd OS HR (95% CI)
4th line unadjusted	0.657 (0.409 - 1.055) †
IPCW adjustment	0.650 (0.373 - 1.132) †
Simple TSE adjustment	0.618 (0.378 - 1.009) †‡

†Stratified by age (<75 years versus >=75 years) according to IRT; ‡ Assuming normal distribution of ln (HR) with standard error based on standard deviation of bootstrap estimates.
Cut-off date: 27JAN2022. Median follow-up time = 52.44 months. HR<1 favours IsaPd arm
CI – confidence interval; HR – hazard ratio; IPCW – inverse probability of censoring weighting; IsaPd – isatuximab + pomalidomide + dexamethasone; OS – overall survival; Pd – pomalidomide + dexamethasone; TSE – two-stage estimation.

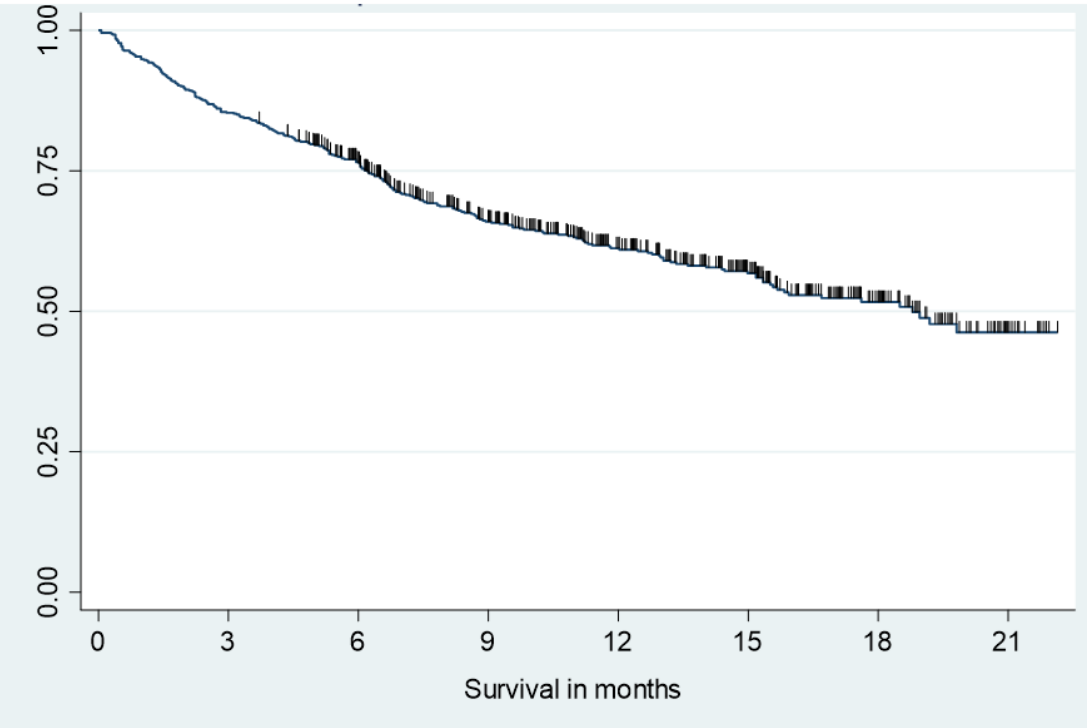
In the Isa SACT cohort (combined CDF and EAMS cohort), the minimum follow-up was 4.8 months (146 days), and the median follow-up was 9.4 months (286 days). The median OS was 18.8 months (95% CI: 15.7, 22.9) (572 days) (Figure 4; CS, pages 70-41).

Figure 3: Kaplan-Meier curves for OS† by treatment group, 4L population (reproduced from CS, Figure 16, page 62)



Source: Sanofi, Clinical study report fourth-line analysis, data on file (2022)[20]
†Cut-off date: 27th January 2022.
IsaPd - isatuximab + pomalidomide + dexamethasone; ITT - intention-to-treat; OS -overall survival; Pd - pomalidomide + dexamethasone

Figure 4: Kaplan-Meier Overall survival plot (N=736), IsaPd (reproduced from CS, Figure 7, page 71)



Source: SACT report (2022)[24]
Notes: One patient died on the same day they started treatment, and as such, they were excluded from the model as their treatment duration was zero days.
SACT - Systemic Anti-Cancer Therapy.

3.2.4.3 Time to definitive treatment discontinuation

The median time to definitive treatment discontinuation was significantly delayed in the IsaPd arm of the 4L population ([redacted]) relative to the Pd arm ([redacted]); stratified HR [redacted] (95% CI: [redacted]), *p*=[redacted].[1]

3.2.4.4 Time to subsequent treatments

No direct comparison data on this outcome was reported. The CS reports on SACT data relating to time to subsequent treatments. In the CDF cohort, the median time from a patient's last IsaPd cycle in SACT to their next treatment was 19 days, the median time from a patient's first IsaPd cycle in SACT was 133 days, and 101/662 (15%) treated with IsaPd received subsequent therapies after the patient's last IsaPd cycle.[1] In the EAMS cohort, the median time from a patient's last IsaPd cycle in SACT to their next treatment was 25.5 days, the median time from a patient's first IsaPd cycle in SACT to their next treatment was 179 days, and 22/75 (29%) patients treated with IsaPd received subsequent therapies after the patient's last IsaPd cycle.[1]

3.2.4.5 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 was maintained over the course of treatment in both arms, although it worsened slightly at the end of treatment, and slightly more so in the IsaPd arm than the Pd arm (CS, Tables 18 and 19, pages 66-67).[1] The company urges caution in interpreting the results due to a small sample size and absence of significance testing.

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, and scores were maintained over time, with both treatments having a reduced HRQoL at the end of treatment, presumably due to disease progression, and slightly more so in the IsaPd arm than the Pd arm (CS, Table 20, page 68).[1] The company urge caution in interpreting the results due to a small sample size and absence of significance testing.

3.2.4.6 Safety and tolerability

IsaPd appears to be generally well tolerated as of the final analysis. At 4L, a greater proportion of patients in the IsaPd arm than the Pd arm experienced grade ≥3TEAEs (90.2% versus 74.1%, respectively), treatment-emergent serious adverse events (80.4% versus 58.6%, respectively), and serious treatment-related adverse events (39.2% versus 22.4%, respectively). However, the incidence of grade 5 (fatal) events was similar in the IsaPd (9.8%) and the Pd arm (10.3%), as was treatment discontinuation due to a TEAE (13.7% versus 19.0% in the IsaPd and Pd arms, respectively). An overview of TEAE rates in the 4L population is provided in the CS, Table 29.[1] In response to clarification question A15, the company provided rates of specific TEAEs by system organ class for the safety population are provided.[13]

3.2.4.7 Subgroups

Consistent with the current NICE recommendation [TA658] and decision problem relevant to this appraisal[8] of the use of IsaPd as a 4L treatment for RRMM, post-hoc analyses have been provided for the 4L sub-population of the ICARIA-MM study.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No studies were used by the company to inform an indirect comparison or multiple treatment comparison. For the comparison against Pd data from the ICARIA-MM study was used directly. For the comparison with daratumumab monotherapy the company explored the use of data from SIRIUS, but as explained in 3.4.2 it was not possible to provide robust estimates of clinical efficacy and SACT data were used instead to perform a naïve indirect comparison.

3.4 Description and critique of the indirect and mixed treatment comparison

3.4.1 IsaPd versus Pd (original submission)

The company did not undertake evidence synthesis of IsaPd compared with Pd, as the efficacy data were available from the 4th line subgroup population in ICARIA-MM. The EAG agrees with using this subgroup population from the ICARIA-MM trial to inform the relevant efficacy results.

3.4.2 IsaPd versus daratumumab monotherapy

The company undertook an exploratory analysis of IsaPd compared with daratumumab monotherapy based on a naïve comparison between the IsaPd SACT data and the daratumumab monotherapy SACT data. The company listed the following reasons for not considering the results from an unanchored matching-adjusted indirect comparison (MAIC) based on ICARIA-MM and SIRIUS: the ITT population from ICARIA-MM had to be used to retain a suitable effective sample size; that there was a large reduction in ESS (n=5) when all available characteristics are adjusted for in MAIC; and that the weighted population does not reflect the population relevant to the decision problem (most patients were at 6th line of treatment or later).

The SACT database includes 737 patients being treated with IsaPd over 28 months from December 2019 to March 2022; and includes 2,301 patients being treated with daratumumab monotherapy over 34 months from January 2018 to November 2020. Because individual patient-level data (IPD) are not available from SACT, the company used digitised KM SACT data to estimate treatment effect for OS and time to treatment discontinuation (TTD). The results are reproduced in Table 10, with the company assuming for both IsaPd and daratumumab monotherapy that PFS was equal to TTD.

The most recent update of the SLR (see the company's response to clarification question A3[13]) identified two further studies that include a daratumumab monotherapy arm: APOLLO and LIGHTHOUSE. However, the EAG acknowledges that, due to the small sample size (in particular of 4th line subgroups), the results of a naïve ITC between ICARIA-MM and APOLLO, and of a MAIC between ICARIA-MM and LIGHTHOUSE would be highly uncertain.

Table 10: Hazard ratios and event counts for comparison of IsaPd SACT and daratumumab SACT for OS and TTD (reproduced from Table 28 of CS)

	OS	TTD
HR estimate, IsaPd versus daratumumab monotherapy	0.880	0.601
95% CI	0.777, 0.997	0.539, 0.671
P-value	0.0445	<0.0001
Isatuximab	N=736, Events=309	N=736, Events=390
Daratumumab	N=2,300, Events=1367	N=2300, Events=1,839

CI - confidence interval; HR - hazard ratio; OS - overall survival; SACT - systemic anti-cancer therapy; TTD - time to discontinuation.

The results in Table 10 represent a naïve comparison. The company correctly states that such comparisons are prone to bias as no adjustment is made for difference in patient characteristics between the sources. The company highlights a number of limitations that includes: SACT data had missing data and coding may not always be accurate; subsequent therapies may confound the outcomes; and that the data collection period for IsaPd overlapped with the first wave of the COVID-19 pandemic which may have impacted on clinical outcomes.

The EAG agrees with the company on the use of SACT data to inform the relative treatment effect of IsaPd compared with daratumumab monotherapy instead of using the unanchored MAIC, however the EAG cautions that the treatment effects derived from the naïve comparisons could be confounded due to the limitations highlighted by the company. Clinical advice to the EAG suggests that because data collection in SACT was earlier for daratumumab monotherapy than for IsaPd, this potentially means that the patients being treated with daratumumab monotherapy in SACT are less pre-treated and would be easier to achieve disease control; the results could therefore be favourable to daratumumab monotherapy.

3.4.3 IsaPd versus Pd (AFC)

After the factual accuracy check, the company submitted additional real-world evidence from a retrospective study using the Cancer Analysis System (CAS) database to inform the effectiveness of Pd at 4th line of therapy.[25] The CAS database comprises the SACT dataset, the Cancer Outcomes and Services Dataset and other linked datasets such as the National Radiotherapy Dataset. This retrospective study uses data from the 1st of January 2014 to the 31st of August 2021. The SACT-treated cohort was used to inform the results for pomalidomide. It was assumed that patients received pomalidomide also received dexamethasone. The SACT-treated cohort was defined as "*All eligible patients with MM who*

received at least one SACT, excluding patients who had received (at any line of treatment [LoT]) a drug which was on the CDF list at the time of analysis."

Because line of treatments (LoTs) is not directly recorded/defined in the CAS dataset, the company used a novel algorithm based on the IMWG criteria to combine SACT agents and regimens into LoTs. The details of the algorithm can be found in the additional evidence submitted by the company.[25]

The company reports that 782 patients received 4 or more LoTs in the SACT-treated cohort and 182 (23.3%) received pomalidomide with outcome data available for 175 patients. The dataset for pomalidomide as 4th line+ from this analysis is named AFC Pd SACT in the rest of this report.

The company states that patient baseline characteristics are not available for patients who received pomalidomide within the 4th LoT because "*SACT regimen-specific patient demographic and clinical characteristics were not collected within this study.*" Age and ECOG for the whole 4th line+ SACT-treated cohort, ICARIA-MM 4th line, IsaPd SACT and daratumumab monotherapy SACT are presented in Table 6 in the additional evidence submitted by the company.[25]

A naïve comparison of FAC Pd SACT and IsaPd SACT was performed by the company. IsaPd SACT data used in this comparison are the same as the one used when comparing with daratumumab monotherapy. The description of this dataset can be found in Section 3.4.2.

Results for treatment duration, time to next treatment or death, and OS from AFC Pd SACT and IsaPd SACT where relevant are summarised in Table 11.

Table 11: Results for FAC Pd SACT vs IsaPd SACT (adapted from additional evidence Table 8 to Table 10)

Cohort	Median TD, months (95% CI)	Median TTNTD, months (95% CI)	Median OS, months (95% CI)	Number of patients
Pomalidomide SACT	3.2 (2.7, 4.1)	4.70 (3.91, 5.98)	6.3 (4.6, 7.8)	175
IsaPd SACT	8.9 (7.3, 10.8)	NE	18.8 (15.7, 22.9)	736

CI - confidence interval; IsaPd - isatuximab with pomalidomide and dexamethasone; SACT - Systemic Anti-Cancer Therapy; TD- treatment duration; TTNTD - time to next treatment or death; OS - overall survival; NE - not evaluated.

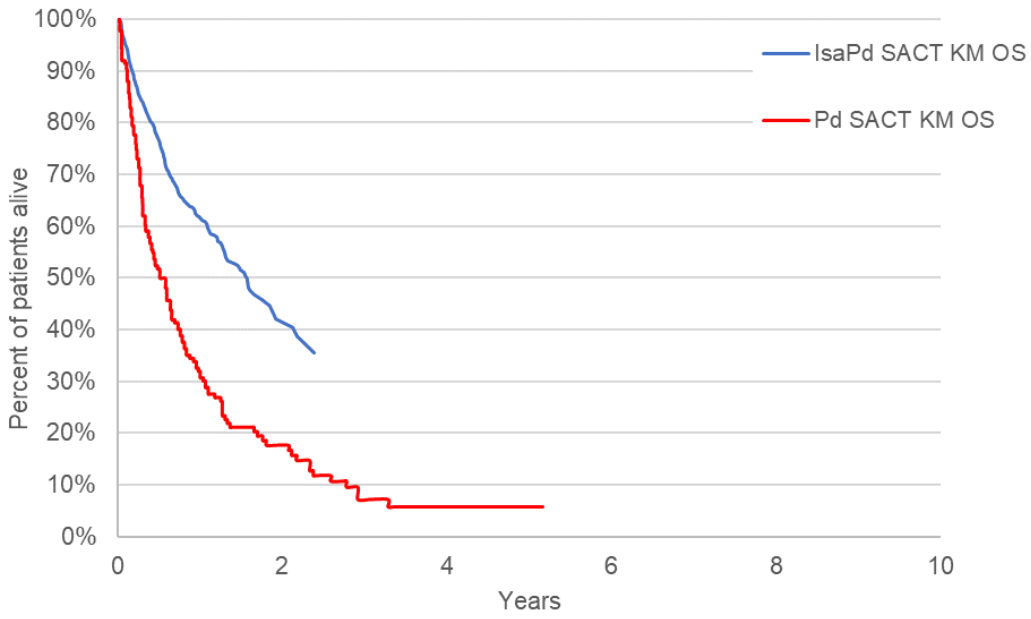
Reconstructed SACT treatment duration and overall survival are reproduced in Figure 5 and Figure 6. The EAG notes that the IsaPd SACT KM OS presented in additional evidence Figure 4 (reproduced in Figure 6) does not appear to be the same as the IsaPd SACT KM OS presented in CS Figure 7 (reproduced in Figure 7) with differences including the shape of the tail and follow-up length. The EAG

also notes that Figure 6 was plotted by the company using reconstructed IPD whereas Figure 7 was extracted directly from SACT data using SACT IPD.[24]

Figure 5: Reconstructed SACT Treatment duration – Kaplan-Meier curves by treatment group: IsaPd and Pd (reproduced from additional evidence Figure 3)

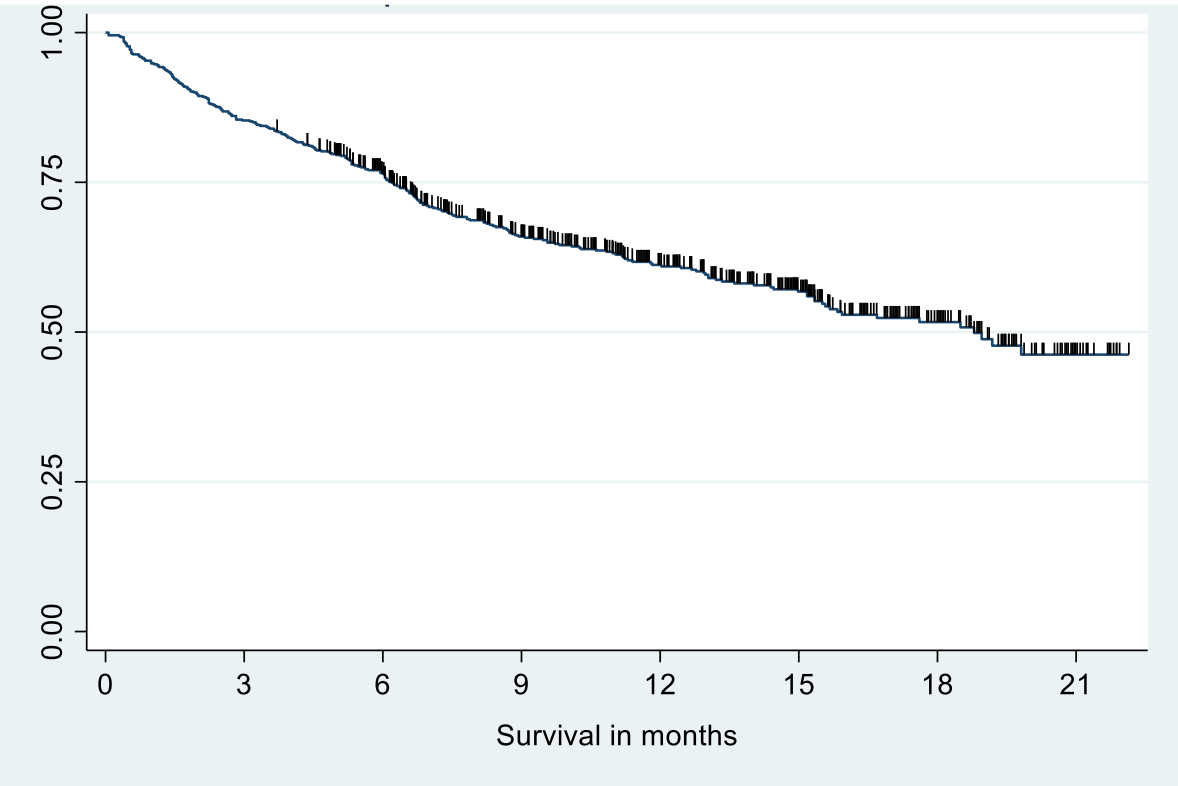
IsaPd - isatuximab with pomalidomide and dexamethasone; KM - Kaplan-Meier; Pd - pomalidomide plus dexamethasone; SACT - systemic anti-cancer therapy; TTD - time to discontinuation.

Figure 6: Reconstructed SACT OS - Kaplan-Meier curves by treatment group: IsaPd and Pd (reproduced from additional evidence Figure 4)



IsaPd - isatuximab with pomalidomide and dexamethasone; KM - Kaplan-Meier; Pd - pomalidomide plus dexamethasone; SACT - systemic anti-cancer therapy; OS - overall survival.

Figure 7: Kaplan-Meier curves: SACT OS IsaPd (reproduced from CS Figure 7)



The EAG disagrees with the company's approach on using the naïve indirect comparison for Pd and IsaPd based on AFC Pd SACT and IsaPd SACT without adjustment instead of the head-to-head RCT (the ICARIA-MM trial) to inform the relative treatment effect of IsaPd versus Pd.

The EAG's concerns on the naïve indirect comparisons for Pd and IsaPd are summarised as follows. There may be substantial difference in populations between AFC Pd SACT and IsaPd SACT. AFC Pd SACT was informed by a subset of the 4th line+ SACT-treated cohort with patients receiving pomalidomide from the CAS dataset (January 2014 to August 2021), which excludes CDF-treated patients. It is unclear the proportion of patients receiving Pd at 4th line in AFC Pd SACT as the data contains 4th line+ patients. The SACT-treated cohort excluded 4,089 patients who received drugs in the CDF. As the company has rightly pointed out "*CDF treated patients were generally younger, diagnosed more recently, had lower comorbidity scores, and better functional status*", therefore, patients in AFC Pd SACT may be less healthy compared to the patients included in IsaPd SACT. The EAG also notes that isatuximab is provided intravenously, whereas Pd is an oral treatment. If patients were considered too frail to receive isatuximab then there could be a selection bias in the treatment groups with healthier patients receiving IsaPd and less healthy patients receive Pd. The EAG believes that there is considerable potential for bias in the naïve comparison which disfavours Pd.

Defining the line of treatments in the SACT dataset is challenging, which is confirmed by the EAG's clinical advisors. The company states that "*some misclassification of LoTs is expected due to deviations from recommended treatments, unexpected delays, or inaccuracies in recording, as perhaps expected in routine clinical practice*". The EAG notes that it is unclear the impact of potential misclassification of LoTs on the relative treatment effect derived from the naïve comparison.

Daratumumab monotherapy SACT data were collected during the period of managed access via the SACT database (January 2018 to November 2020) and include 2,301 patients. The SACT-treated cohort (used to inform AFC Pd SACT, January 2014 to August 2021) includes 606 patients who received daratumumab with 245 at 4th line. The EAG is unclear the reasons for the marked difference in daratumumab-treated patients in the SACT-treated cohort and SACT database (used in the CS) given that the study period for the SACT-treated cohort covers the study period for the CS SACT database which may question further the generalisability of AFC Pd SACT presented in the additional evidence to UK practice.

The company claims that "*the patient characteristics observed across the SACT datasets (4th LoT SACT [Pom], IsaPd SACT and daratumumab monotherapy SACT) are broadly comparable, where data is available*." The EAG notes that only age and ECOG were available to compare across these datasets. The EAG believes that there was no evidence to suggest that population across the SACT datasets (AFC Pd SACT, IsaPd SACT and daratumumab monotherapy SACT) are comparable given that (i) the comparison was made between the whole 4th line+ SACT-treated cohort, IsaPd SACT and daratumumab monotherapy SACT; and (ii) only two patient characteristics (age and ECOG) were available to compare and ECOG was poorly recorded in the SACT datasets. The EAG highlights that AFC Pd SACT excludes patients who received drugs through the CDF, whereas this exclusion does not apply in IsaPd SACT and daratumumab monotherapy SACT.

Overall, the EAG believes that the company's naïve comparison of Pd and IsaPd are prone to bias as the population for Pd may be less healthy than the population for IsaPd and no adjustments were conducted for potential confounders.

3.5 Additional work on clinical effectiveness undertaken by the EAG

No additional work on clinical effectiveness was undertaken by the EAG.

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,[9, 15] a Phase III open-label RCT. The EAG 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 EAG 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 for the final analysis (14th March 2022), which is a recommended outcome according to the EMA.[18] In the 4L population, the median PFS was greater in the IsaPd arm (12.39 months [95% CI: 7.425, 27.663]) than in the Pd arm (6.54 [95% CI: 4.468, 10.086]), and the stratified (by age) HR was 0.536 (95%: CI 0.343, 0.840), which the CS states represents a 46.4% risk reduction of disease progression or death in favour of IsaPd compared with Pd.[2] The EMA suggests that OS should demonstrate a trend towards superiority if PFS is used as a primary outcome.[18] Mortality events were reported in 61.5% and 72.4% of 4L patients in the IsaPd and Pd arms, respectively, at the cut-off date for the final analysis (27th January 2022), with a median OS of 33.28 months (95% CI :18.431, 54.275) in the Isa Pd arm and a median OS of 17.71 months (95% CI: 11.565, 27.532) in the Pd arm (stratified HR 0.657 [95% CI 0.409, 1.055], p=0.080), which indicates greater OS in the IsaPd arm. 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. There was 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 EAG 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.

There is a lack of head-to-head evidence comparing IsaPd versus daratumumab monotherapy. A naïve comparison of the IsaPd SACT and daratumumab SACT data was used to inform the relative treatment effect. The EAG notes that the treatment effects derived from the naïve comparisons are highly uncertainty due to the lack of randomisation and adjustments for potential confounders.

After factual accuracy check, the company submitted additional evidence and proposed to use the naïve comparison of AFC Pd SACT and IsaPd SACT to inform the relative treatment effect of IsaPd versus Pd instead of the data from the head-to-head trial (ICARIA-MM). The EAG believes that the company's naïve comparison of Pd and IsaPd is prone to bias due to the population for Pd may be poorer than the population for IsaPd used in the analysis and no adjustments were conducted for potential confounders.

4 COST EFFECTIVENESS

This chapter presents a summary and critique of the company's health economic analyses of IsaPd 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 EAG, respectively. Section 4.5 presents a brief discussion of the key drivers of the ICER.

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, and further versions were received that added additional statistical distributions and that fixed errors in the probabilistic analyses. For brevity, this report will only refer to the latest model (and results) received, unless explicitly stated otherwise.

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 an initial de novo SLR in October 2018, followed by a revised and updated search in November 2022. The three-in-one de novo systematic literature review search was to identify literature for i) published cost-effectiveness studies of adults diagnosed with RRMM who have failed at least two lines of treatment (CS Appendix G), ii) HRQoL studies (CS Appendix H) with separate searches in the November 2022 update, and iii) Cost and healthcare resource use studies with separate searches in the November 2022 update (CS Appendix I).

A clarification question concerning the clinical effectiveness searches was raised with the company (clarification letter A4, page 3) to confirm that no new and relevant studies have been published since the last updated search (database searches in November 2022 and hand searching in December 2022). In response, and as of October 2023, the company has undertaken a pragmatic and partial update of the SLR search (company response A4, pages 8-11) of electronic database search, HTA agency search, and Cost Effectiveness Analysis Registry. The company reported that 56 records were retrieved, only three were screened in full-text, and none were included as described in Table 8 of the company's clarification response (page 11). The company concluded that no further studies were published since the last searches in November 2022. Given the timeframe, the EAG did not request that the HRQoL and cost

and healthcare resource use searches be updated, so their searches cover the period up to November 2022.

In all three types of searches (Appendix G-I), the company searched all the relevant electronic bibliographic databases up to November 2022 (Appendix G.1. Identification of studies): MEDLINE, including MEDLINE in Process (via Ovid), EMBASE (via Ovid), NHS Economic Evaluation Database (via CRD until June 2019), and Health Technology Assessment database (via CRD until June 2019). The company hand-searched the bibliographies of relevant systematic reviews and network meta-analyses to identify other new studies for inclusion.

The company searched several key conference abstract websites (up to December 2022): ASCO, ASH, EHA, ESH, and ESMO. In addition, six health technology assessment agencies were searched (up to December 2022): NICE, SMC, CADTH, ICER, PBAC, and HAS. Several economic repositories and resources were searched (up to December 2022): Cost Effectiveness Registry, EconPapers (via RePEc), EQ-5D website, SCHARRHUD Database, and INAHTA HTA database.

The company's de novo economic SLR searches (Appendix G) in October 2018 were broad by searching for the population (RRMM) combined with the three search filters (economic evaluations, HRQoL, and cost and resource use), whereas the subsequent update searches for economic evaluations combined the population and interventions and comparators (Isatuximab, Bortezomib, Daratumumab, Dexamethasone, Panobinostat, and Pomalidomide) in June 2019, November 2022, and October 2023 that are within the NICE scope. The intervention and comparators were not included in the updated HRQoL, and cost and healthcare resource searches were kept broad by combining the population with a sensitive search filter.

Overall, the CS economic, quality of life, cost, and resource use SLR search strategies are transparent and fully reported. There were no errors in the search, and the EAG considers that the search is comprehensive.

4.1.2 Summary of company's review findings

In its original review the company identified twenty studies that met the inclusion and exclusion criteria, this search was updated in June 2019 and November 2022 with four additional studies identified. The company stated that eight of the studies were relevant for this STA. Four of these were company submissions to NICE: daratumumab monotherapy both for the initial submission[26] and on exit from the CDF[5]; and pomalidomide with low-dose dexamethasone;[27] and the previous submission for isatuximab with pomalidomide and dexamethasone.[28] One submission was to the All Wales Medicines Strategy

Group for pomalidomide,[29] and three were to the Scottish Medicines Consortium relating to daratumumab monotherapy[30], pomalidomide[31], and isatuximab.[32] The company used the model structure it had used previously which was acceptable to the EAG.

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® which was updated during the clarification process. Only the latest version of the company's model and its results are discussed in this document. The EAG identified several limitations within the model which the EAG believed that if amended would make minimal impact on the ICERs; these have not been documented for brevity reasons.

A summary of the company's base case model is summarised in Table 12. The company's base case analysis assesses the ICER expressed in terms of cost per QALY gained of IsaPd compared with Pd in patients with RRMM who have received 3 lines of prior therapies including lenalidomide and a PI. An exploratory analysis in the same population is provided to estimate the ICER of IsaPd compared with daratumumab monotherapy.

Table 12: Summary of company's base case (and exploratory) 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	40 years, assumed to represent a patient's lifetime
Intervention	Isatuximab (plus pomalidomide and dexamethasone) (IsaPd)
Comparator	Pomalidomide and dexamethasone (Pd). Daratumumab monotherapy was used in an exploratory analysis
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 (2020/2021); 2022 (British National Formulary) and 2023 (electronic market information tool) 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 economic analysis was undertaken from the perspective of the NHS and Personal Social Services (PSS) over a 40-year (lifetime) horizon. Unit costs are valued at 2020/2021 prices, although the drug costs use either 2022 or 2023 prices. Health outcomes and costs are discounted at a rate of 3.5% per annum as recommended by NICE.

Population

The modelled population relates to adult patients with RRMM, who have received 3 lines of prior therapies, including lenalidomide and a PI. This population is consistent with a subgroup of the ICARIA-MM study,[15] the final NICE scope[8] and the marketing authorisation for isatuximab.[33] At model entry, patients are assumed to have a mean age of 65.1 years, a body surface area (BSA) of 1.8m^2 and with 51.8% of patients are assumed to be male.[2] The company states (CS, page 95) that *"although the patients entering the model are younger than those treated in the CDF*, *evidence from ICARIA-MM demonstrated consistent outcomes across all pre-specified subgroups including age (<75 years versus ≥75 years".*[1] However, the EAG 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 EAG 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. Pomalidomide is assumed to be administered orally at a dose of 4mg on days 1 to 21 of every four-week cycle. Dexamethasone is assumed to be administered orally (or IV, if the oral route is not possible) at a dose 40mg (20mg if the patient is 75 years or older) on days 1, 8, 15 and 22 of every four-week cycle. In the IsaPd arm of ICARIA-MM, 13.5% of patients received a 20mg dose of dexamethasone and 25.5% received treatment via IV.

The model also considers medication used prior to isatuximab infusion with the objective of reducing the risk and severity of infusion reactions. Such interventions are provided in Section B.3.2.4.1.1 of the CS, although the costs associated with these interventions are relatively trivial compared to the costs of isatuximab and pomalidomide.

Comparators

The comparator evaluated within the company's base case analyses 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. In the Pd arm of ICARIA-MM, 15.5% of patients received a 20mg dose of dexamethasone and 0% received treatment via IV.

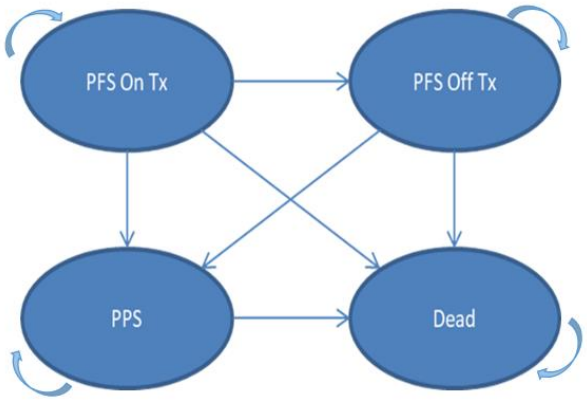
An exploratory analysis compares with daratumumab monotherapy. Daratumumab monotherapy was assumed to be administered subcutaneously as follows: 16 mg/kg infusion on days 1, 8, 15 and 22 of each four-week cycle in cycles 1 and 2, then on days 1 and 15 of each four-week cycle in cycles 3–6, then day 1 of each four-week cycle thereafter. Premedication treatments were given alongside daratumumab monotherapy, but these are relatively trivial compared to the costs of daratumumab.

Drug acquisition costs for IsaPd, Pd and daratumumab monotherapy over the patient's lifetime are based on the probability of patients remaining on each treatment based on TTD functions.

4.2.2 Model structure and logic

The general structure of the company's economic model was described in the original CS (pages 96-98),[2] as a partitioned survival model approach, based on four health states: (i) progression-free on treatment; (ii) progression-free off treatment; (iii) post-progression, and (iv) death (see Figure 8). It is possible to remain in the same health state between cycles.

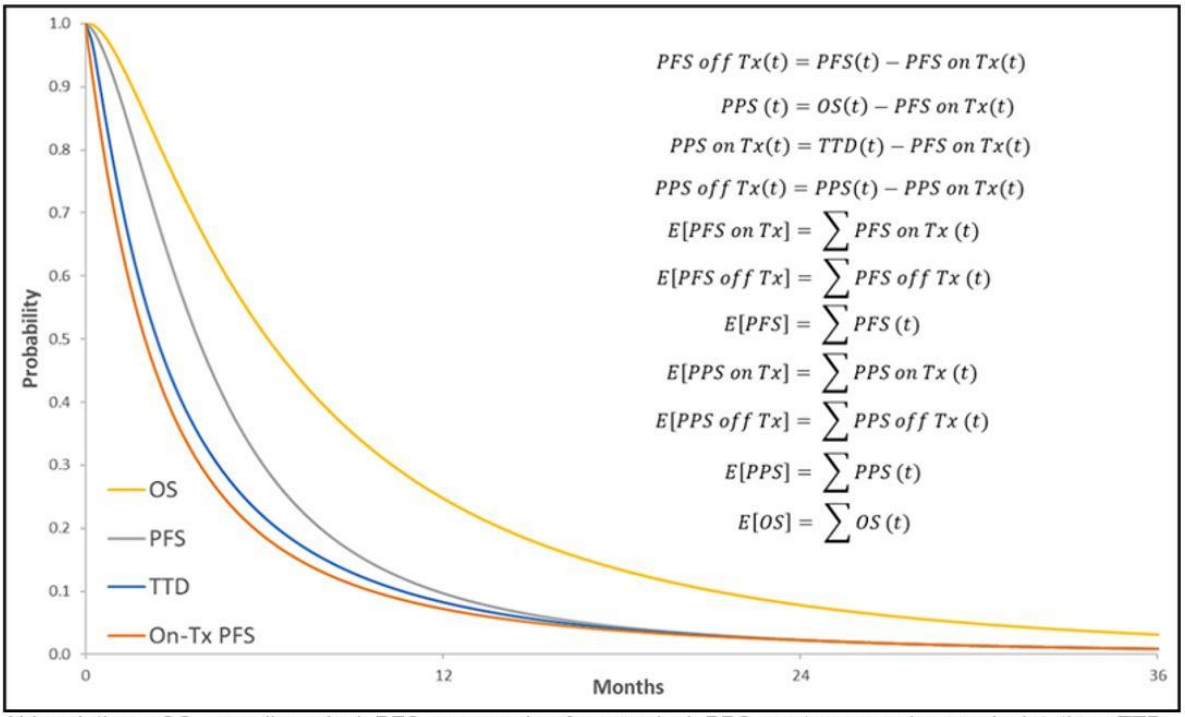
Figure 8: Company's model structure (reproduced from initial CS, Figure 20)



PFS – Progression-free survival; PPS – Post-progression survival; Tx - Treatment

An alternative schematic was provided in the latest CS which is replicated in Figure 9. Both are informative in different ways so have been included for the reader.

Figure 9: Company's model structure (reproduced from CS, Figure 8)



Abbreviations: OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; t, time; TTD, time to discontinuation; Tx; treatment.

Utility in the PFS and PD health states was assumed to be independent of whether or not the patient is on treatment. 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, however, the model structure allows for different utilities to be included in the PD health state dependent on whether a person was on, or off, treatment. For simplicity, the EAG reports parameters as though the model was constructed as a three-state partition survival model and does not discuss the PFS off treatment health state further. The EAG comments that the model was relatively cumbersome and had a file size over 55 Megabytes, due to functionality options that are not used within this decision problem.

Within the company's model, patients enter the model in the progression-free and alive state and receive 4L treatment. For IsaPd and Pd, PFS, TTD and OS are modelled using treatment-specific parametric distributions fitted to time-to-event data for patients from the 4L subgroup in ICARIA-MM RCT.[15]

For the exploratory analysis comparing IsaPd with daratumumab monotherapy SACT data is used in a naïve comparison as described in Section 3.4.

A mortality constraint is applied in all analyses to ensure that the probability of survival for the modelled population does not exceed that of the general population of the UK.[34]

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*.
- Post-progression survival (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 (PFS or PPS) and the type of treatment received (IsaPd, Pd or daratumumab monotherapy). 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 Hernandez Alava *et al*.[35] EQ-5D-3L estimates were adjusted for patient-aging using the relationship reported by Hernandez Alava *et al*.[36] The company includes a QALY decrement to capture the decline in HRQoL during the terminal phase of the disease, which was also derived from ICARIA-MM data. The model includes QALY losses associated with AEs for IsaPd, Pd and daratumumab monotherapy.

The model includes costs associated with: (i) drug acquisition, administration, and pre-medication; (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, the assumed 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, 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 40 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 exploratory analyses are presented for the comparison of IsaPd versus daratumumab monotherapy.

4.2.3 Key assumptions employed in the company's model

The company's model employs the following key assumptions in its base case:

- The PAS discount was applied to isatuximab. Following prevailing NICE guidance, list prices were used for all other drugs;
- For the comparison with Pd, restricted cubic spline (RCS) Weibull distributions were used for modelling PFS, jointly-fitted lognormal distributions were used for TTD; and jointly-fitted lognormal distributions were used for OS;
- In the base case AFC comparison with Pd, PFS and TTD were assumed to follow lognormal distributions for IsaPd and a log-logistic distribution for Pd. OS was assumed to follow a lognormal distribution for both IsaPd and Pd;
- For the exploratory comparison with daratumumab monotherapy, PFS and TTD were assumed to follow lognormal distributions for IsaPd but follow generalised gamma distributions for daratumumab. OS was assumed to follow a lognormal distribution for IsaPd, whereas this was a Weibull distribution for daratumumab;
- Drug acquisition costs for IsaPd and comparators are modelled using the TTD survival functions;
- 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;
- HRQoL is assumed to be conditional on 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 [redacted] (estimated from the GEE model) is applied for 12 weeks 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;[15, 37, 38]
- The proportion of patients receiving 5L treatment were based on data from SACT with treatments included if they accounted for 2% or greater of subsequent treatments. The mean duration of each therapy was based on external data;[39]
- The cost of terminal care was assumed to be the same irrespective of the treatment received (£981.41), based on a previous submission to NICE for pomalidomide[40] inflated to current values;
- The model considers only AEs that were reported in ≥5% of patients that were judged to be Grade 3 or higher in severity. For IsaPd and Pd these came from the treatment arms of ICARIA-MM.[15] For daratumumab monotherapy Mateos *et al*.[41] was used as was the case in the manufacturer's submission to NICE.[42] costs sourced from NHS Reference Costs 2020/21.[43]

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 13. These are discussed in detail in the subsequent sections.

Table 13: Summary of evidence used to inform the company's base case analysis and comparison of IsaPd and exploratory comparison with daratumumab monotherapy

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[9]
OS – IsaPd and Pd	Jointly-fitted lognormal distributions fitted to the observed OS data for the 4L subgroup in ICARIA-MM[9]
PFS – IsaPd and Pd	RCS Weibull models fitted to the observed PFS data for the 4L subgroup in ICARIA-MM[9]
TTD – IsaPd and Pd	Jointly-fitted lognormal distributions fitted to the observed TTD data for the 4L subgroup in ICARIA-MM[9]
Age, base case AFC	Values from SACT dataset
OS – IsaPd and Pd	Lognormal distributions fitted to SACT data
PFS – IsaPd and Pd	PFS was assumed to be equal to TTD for both treatments
TTD – IsaPd and Pd	Estimated from SACT data. A lognormal distribution for IsaPd and a log-logistic distribution for Pd
Mortality – general population constraint*	Derived from interim life tables for England 2018-2020[44]
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[9] (mapped to EQ-5D-3L using Hernandez *et al*[35])
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 Hernandez Alava *et al*[35])
Duration of the end-of-life HRQoL decrement*	Based on previous literature and review of the data from ICARIA-MM[9, 37, 38]
HRQoL age-adjustment*	Age- and gender-matched general population utilities based on published UK population norms from Hernandez Alava *et al*.[36]
The proportion of patients experiencing AEs - IsaPd and Pd	Based on data from 4L subgroup on IsaPd or Pd in ICARIA-MM[9]
AE disutility – IsaPd and Pd	The disutility associated with AEs were assumed to be captured in the data from ICARIA-MM[9]
Costs associated with AEs – IsaPd and Pd	AE frequencies based on ICARIA-MM;[9] unit costs taken from NHS Reference Costs 2020/21[43]
Drug acquisition costs – IsaPd and Pd	Unit costs from Electronic Market Information Tool (eMIT)[45] and British National Formulary (BNF),[46] estimates of BSA, weight and RDI obtained from ICARIA-MM[9]
Drug administration costs – IsaPd and Pd	Unit costs taken from NHS Reference Costs 2020/21[43]
Disease management costs (follow-up and monitoring) – IsaPd and Pd	Clinician input (see Table 50 of the CS)
Probability of receiving each of the subsequent therapies considered– IsaPd and Pd	Values from SACT dataset. See Table 46 of the CS.

Parameter group	Source
Post-progression treatment costs (subsequent therapy) – IsaPd and Pd	Unit costs from eMIT[45] and BNF[46]. See Table 48 of the CS
Mean duration of subsequent therapies – IsaPd and Pd	Estimated using data from a Kantar Health Study[47] and assumptions. See Table 49 of the CS.
End of life care costs – IsaPd and Pd	Pomalidomide submission to NICE (TA427),[48] updated to 2022 costs[49]
Additional exploratory analysis – evidence used to inform the comparison of IsaPd and daratumumab monotherapy for 4L. Naïve comparison using SACT data	
OS – IsaPd and daratumumab monotherapy	The OS for IsaPd was assumed to be a lognormal distribution whereas the OS for daratumumab was assumed to follow a Weibull distribution.
PFS – IsaPd and daratumumab monotherapy	PFS was assumed to be equal to TTD for both treatments
TTD – IsaPd and daratumumab monotherapy	The TTD for IsaPd was assumed to be a lognormal distribution whereas the TTD for daratumumab was assumed to follow a generalised gamma distribution
HRQoL for health states – daratumumab monotherapy	The company assumed the same values as for Pd
End of life HRQoL decrement – daratumumab monotherapy	The company assumed the same values as for IsaPd and Pd
Probabilities of patients having AEs - daratumumab monotherapy	Estimates of the probabilities of AEs for daratumumab were taken from Mateos *et al*.[41]
AE disutility – daratumumab monotherapy	The net impact of AEs for daratumumab were estimated based on i) the difference in rates between daratumumab and Pd ii) the utility loss associated with AEs reported in previous NICE submissions and from literature. The durations of AEs were based on the values used in TA510.[50] See Table 38 of the CS.
Costs associated with AEs – daratumumab monotherapy	The company assumed the same values as for IsaPd and Pd
Drug acquisition costs – daratumumab monotherapy	Cost taken from the BNF[46]
Drug administration costs – daratumumab monotherapy	Unit costs taken from NHS Reference Costs 2020/21[43]
Disease management costs (follow-up and monitoring) – daratumumab monotherapy	The frequency of physician visits and blood tests was assumed to be the same as for IsaPd and Pd
Probability of receiving each of the subsequent therapy considered – daratumumab monotherapy	Values from SACT dataset. See Table 46 of the CS.
Post-progression treatment costs (subsequent therapy) – daratumumab monotherapy	Unit costs from eMIT[45] and BNF[46]. See Table 48 of the CS
Mean duration of subsequent therapies – daratumumab monotherapy	The company assumed the same values as for IsaPd and Pd
End of life care costs – daratumumab monotherapy	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; Pd – pomalidomide and dexamethasone; RCS – restricted cubic spline; RDI - relative dose intensity; SACT – systemic anti-cancer therapy; STA – single technology appraisal; TA – technology appraisal.

** Used in all models*

4.2.4.1 *Patient characteristics at model entry*

The model assumes that patients enter the model aged 65.1 years with 51.8% of the modelled cohort is assumed to be male. Patients are assumed to have a mean BSA of 1.8m^2 and to weigh 73.1kg. These characteristics reflect the population of patients who have received three prior lines of treatment (4L) in the ICARIA-MM trial.[15] In the base case AFC[51], the average age of patients was changed to 71.0 years of age although the proportion that were assumed to be male, mean BSA and mean weight remained unchanged.

4.2.4.2 *Description and critique of the company's survival analyses for IsaPd versus Pd (original submission)*

For each of the outcomes used in the economic model (OS, PFS and TTD) comparing IsaPd with Pd, six standard parametric models were fitted (exponential, Weibull, Gompertz, log-logistic, lognormal, and generalised gamma distributions) to the data from ICARIA-MM in the 4th line population. These were fitted both jointly (where one parameter value changed based upon treatment arm which the company referred to as a "*Restricted*" modelling approach) and independently where all parameter values could differ between treatment arms (which the company referred to as an "*Unrestricted*" modelling approach). Survival functions were also estimated RCS models with one knot.

The company states that their preferred base case model was based on goodness-of-fit statistics with the Bayesian information criterion (BIC) as the primary measure of statistical fit, visual comparison with empirical Kapan-Meier survival functions, assessment of the hazard functions and the treatment effect diagnostics and the clinical plausibility of the projected survival functions.

4.2.4.2.1 Overall survival

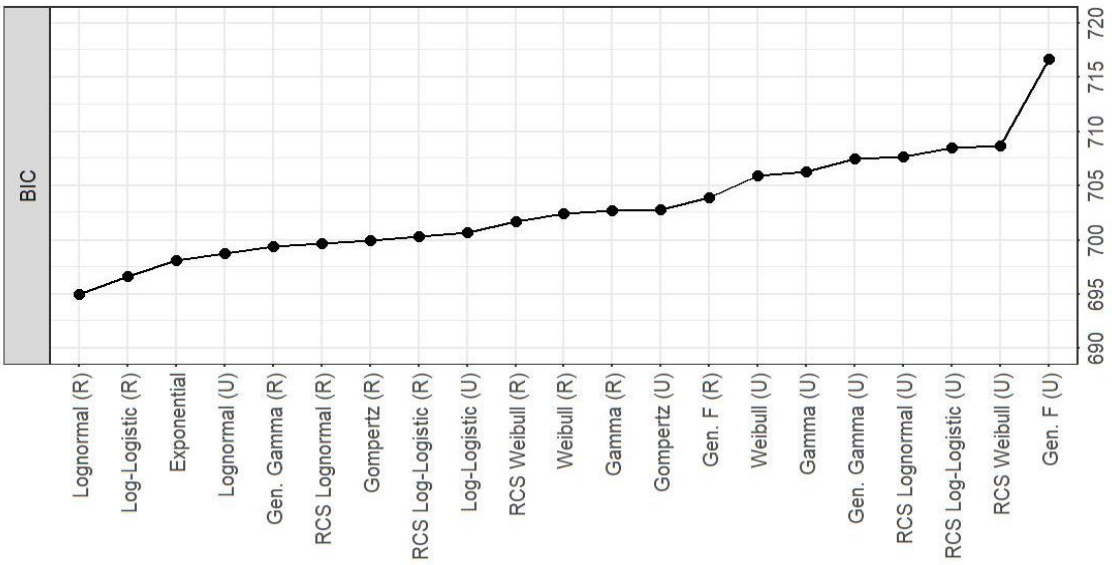
The company considers that both proportional odds and accelerated failure time (AFT) models may be appropriate and chooses the restricted lognormal distribution as the base case to model OS for IsaPd and Pd as this model provides a good statistical (BIC) and visual fit for both arms. The BIC scores for the fits to OS provided within the CS are reproduced in Figure 10. The company used (R) to denote jointly-fitted models with a treatment effect covariate and used (U) to denote models fitted independently to each arm. The plot of the six best-fitting parametric models to the OS KM data are reproduced in Figure 11.

The company notes that clinical opinion of four highly experienced UK haematologists received by the company suggested that "*exponential distribution was likely to better represent expected long-term survival in patients receiving treatment at 4th line in UK clinical practice*". The company considers that the use of exponential model is not appropriate because this model implies a constant hazard and is not supported by the data from ICARIA-MM. However, the company tested using lognormal for

IsaPd and exponential for Pd in a scenario analysis as the company believed that the exponential distribution that the clinicians preferred may apply only to their experience of survival in patients treated with Pd. Alternative survival models were also run in scenario analyses.

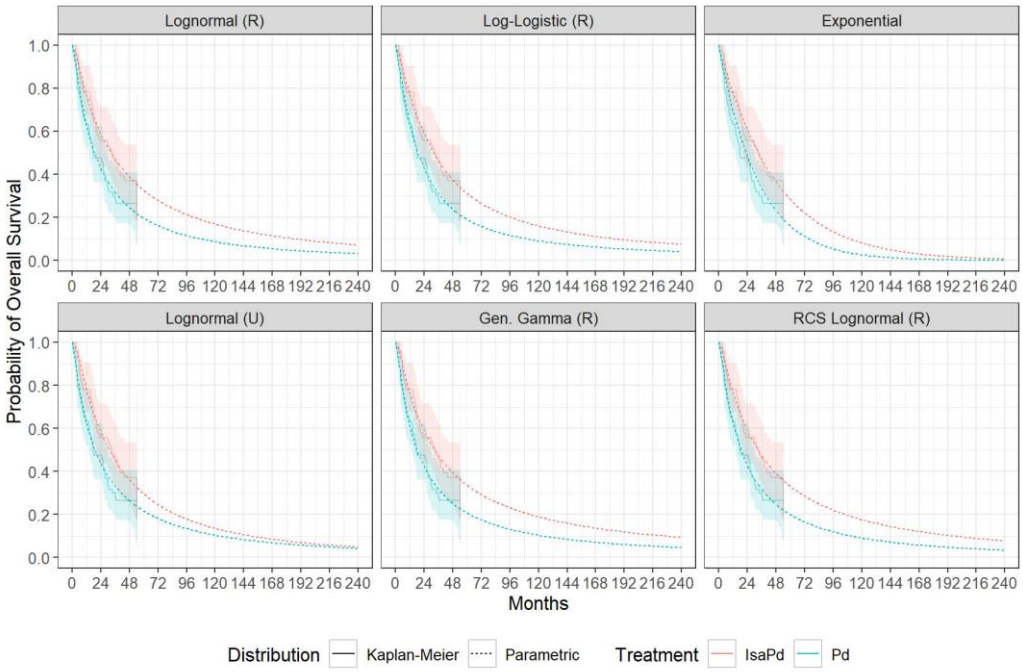
The EAG disagrees with the company's choice of using jointly-fitted modelling approach as this approach assumes that the treatment effect is constant over time, which may be implausible following progression in both arms. More detailed critique on this issue can be found in Section 4.3.2. Clinical advice to the EAG also suggests that the exponential model provides the most plausible long-term extrapolation and that the long-term extrapolation from all other models appear optimistic.

Figure 10: Bayesian Information Criteria fit to OS data for the 4th line population of ICARIA-MM (reproduced from Figure 16 of the CS Appendix R)



BIC – Bayesian Information Criterion; PFS – progression-free survival; R – restricted; RCS – restricted cubic spline; U – unrestricted

Figure 11: Selected model fits to the KM OS data for IsaPd and Pd (reproduced from Figure 13 of the CS)



†General population mortality not applied.
IsaPd – isatuximab + pomalidomide + dexamethasone; OS – overall survival; Pd – pomalidomide + dexamethasone; R – restricted; U – unrestricted

The company also presents a scenario analysis using the TSE adjusted HR based on the ICARIA-MM OS data to account for the fact that daratumumab in 5th line is not permitted in UK clinical practice. The EAG notes that the adjustments were conducted using both IPCW and TSE approach: the TSE approach provides a more favourable HR for IsaPd versus Pd (0.618 with 95% CI: 0.378 to 1.009) compared with the IPCW approach (0.650 with 95% CI: 0.373 to 1.132) (see Table 9). The company notes that these results showed by treated with caution given the small sample size and the assumptions made by both methods.

The EAG also notes that the use of daratumumab after IsaPd or Pd is associated with the biggest difference across the two arms (22.9%); and the difference in the proportion of patients received other therapies which are not permitted in UK clinical practice varies from 0.5% to 10% between the two arms. The EAG agrees with the company's caution regarding the interpretation of the adjusted HRs and notes that the company has not provided justification as to why the TSE-adjusted HR is preferred over the IPCW-adjusted HR. Given that the IPCW-adjusted HR is much closer to the unadjusted HR (0.650 with 95% CI: 0.373 to 1.132 versus 0.657 with 95% CI: 0.409 to 1.055), the EAG believes that the impact on using the IPCW-adjusted HR on the ICER would be minimal.

On inspection, the EAG believes that after applying the TSE-adjusted HR the estimated survival lacks face validity because the estimated survival for Pd does not appear to change and the estimated survival for IsaPd is more favourable than before the adjustment. The EAG would have anticipated that the survival estimates for both IsaPd and Pd would have been less favourable after removing daratumumab at 5th line.

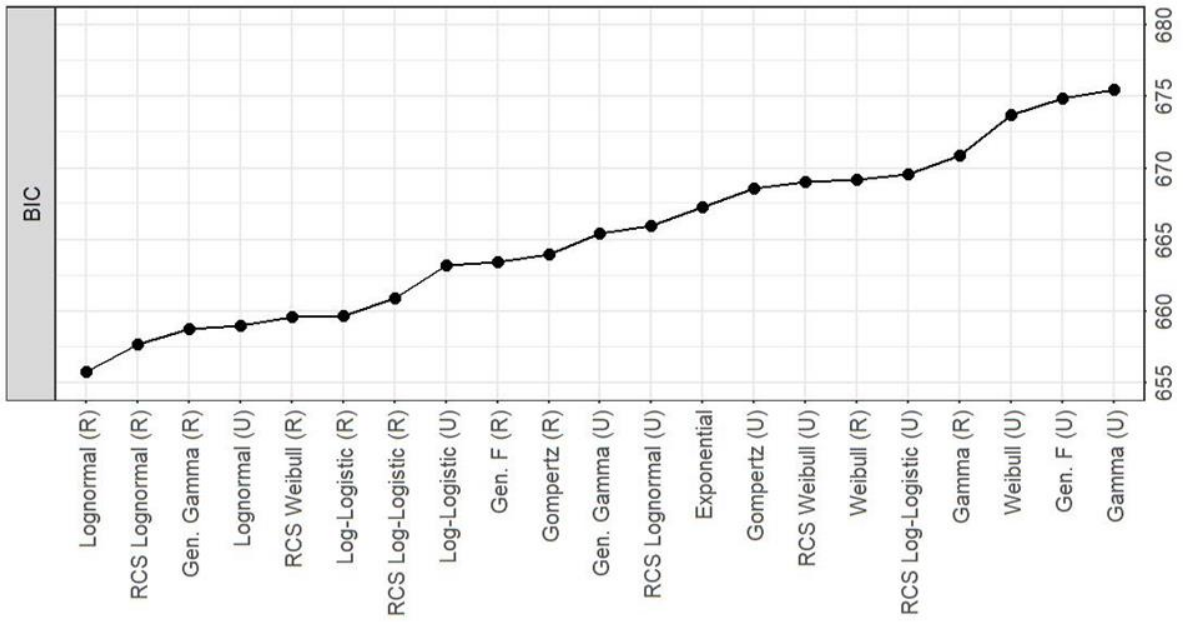
4.2.4.2.2 Progression-free survival

The company considers that proportional hazards (PH) models may be most appropriate and chooses the restricted RCS Weibull model as the base case to model PFS for IsaPd and Pd based on statistical goodness of fit (BIC), visual fit, treatment effect diagnostics and clinical plausibility. The BIC scores for the fits to PFS provided within the CS are reproduced in Figure 12. The plot of the six best-fitting parametric models to the PFS KM data are reproduced in Figure 13.

The company notes that the jointly-fitted RCS Weibull provides PFS below 10% at 3 years, below 5% at 5 years and close to 0% by 10 years and this is reasonbale given the patients are 4th line population. The company also commented that there is no external clincial trial data to validate the long-term PFS predictions for IsaPd.

The EAG notes that the company's jointly-fitted modelling approach assumes that the treatment effect is constant over time, which may not be correct. The EAG notes that independently-fitted lognormal models fits better (a lower BIC) than the jointly-fitted RCS Weibull model (see Figure 12), has equally good visual fit to the data and plausible long-term prediction for Pd (see Figure 12) and does not require a constant treatment effect to be assumed. Based on the above considerations, the EAG prefers the use of independently-fitted lognormal distributions in its base case.

Figure 12: Bayesian Information Criteria fit to PFS data for the 4th line population of ICARIA-MM (reproduced from Figure 17 of the CS Appendix R)



BIC – Bayesian Information Criterion; PFS – progression-free survival; R – restricted; RCS – restricted cubic spline; U – unrestricted

Figure 13: Selected model fits to the KM PFS data for IsaPd and Pd (reproduced from Figure 16 of the CS)

[redacted]

†General population mortality not applied.
IsaPd – isatuximab + pomalidomide + dexamethasone; PFS – progression-free survival; Pd – pomalidomide + dexamethasone; R – restricted; U – unrestricted

4.2.4.2.3 Time to discontinuation

The company considers that AFT models may be most appropriate and chooses the jointly-fitted lognormal model as the base case to model TTD for IsaPd and Pd as this model provides the best statistical (BIC) and visual fit for both arms and provides clinically plausible long-term prediction (<5% remaining on treatment at 10 years in either arm). The BIC scores for the fits to TTD provided within the CS are reproduced in Figure 14. The plot of the six best-fitting parametric models to the TTD KM data are reproduced in Figure 15.

The EAG agrees with the company's base case choice that the jointly-fitted lognormal model appears to provide good statistical goodness of fit and visual fit, and the long-term predictions are plausible. However, the EAG highlights the previously mentioned limitations of using a jointly-fitted modelling approach but notes that changing to independently-fitted models does not have a large impact on the ICER.

Figure 14: Bayesian Information Criteria fit to TTD data for the 4th line population of ICARIA-MM (reproduced from Figure 19 of the CS Appendix R)

BIC – Bayesian Information Criterion; TTD – time-to-treatment discontinuation; R – restricted; RCS – restricted cubic spline; U – unrestricted

Figure 15: Selected model fits to the TTD data for IsaPd and Pd (reproduced from Figure 28 of the CS)

IsaPd – isatuximab + pomalidomide + dexamethasone; TTD – time to discontinuation; Pd – pomalidomide + dexamethasone; R – restricted; U – unrestricted

4.2.4.3 *Description and critique of the company's survival analyses for IsaPd versus daratumumab*

The company uses SACT data to inform the comparison between IsaPd and daratumumab due to the limitations of the MAIC (see Section 3.4). Only OS and TTD are available from SACT data and therefore the company assumes that PFS is equal to TTD which the EAG believes is a reasonable assumption.

For both OS and TTD, initially eight standard parametric models (exponential, Weibull, Gompertz, log-logistic, lognormal, gamma, generalised gamma, and generalised F distributions) and three spline models with one knot (RCS lognormal, RCS Weibull and RCS log-logistic) were fitted independently to IsaPd SACT data and daratumumab SACT data. In response to clarification question B13, the company also provided survival extrapolations using spline models with two and three knots.

4.2.4.3.1 Overall survival

The company chooses the lognormal distribution as the base case to model IsaPd OS based on statistical (BIC) and visual fits. The company notes that the lognormal distribution provides the long-term prediction near the middle of the range of estimates among the models considered, and the predictions (approximately 20% at 6 years, 10% at 14 years and 6% at 20 years) are plausible considering the poor

prognosis and age of the patients. The BIC scores for the fits to OS provided within the CS are presented in Table 14. The plot of the fitted parametric models to the OS KM data are reproduced in Figure 16)

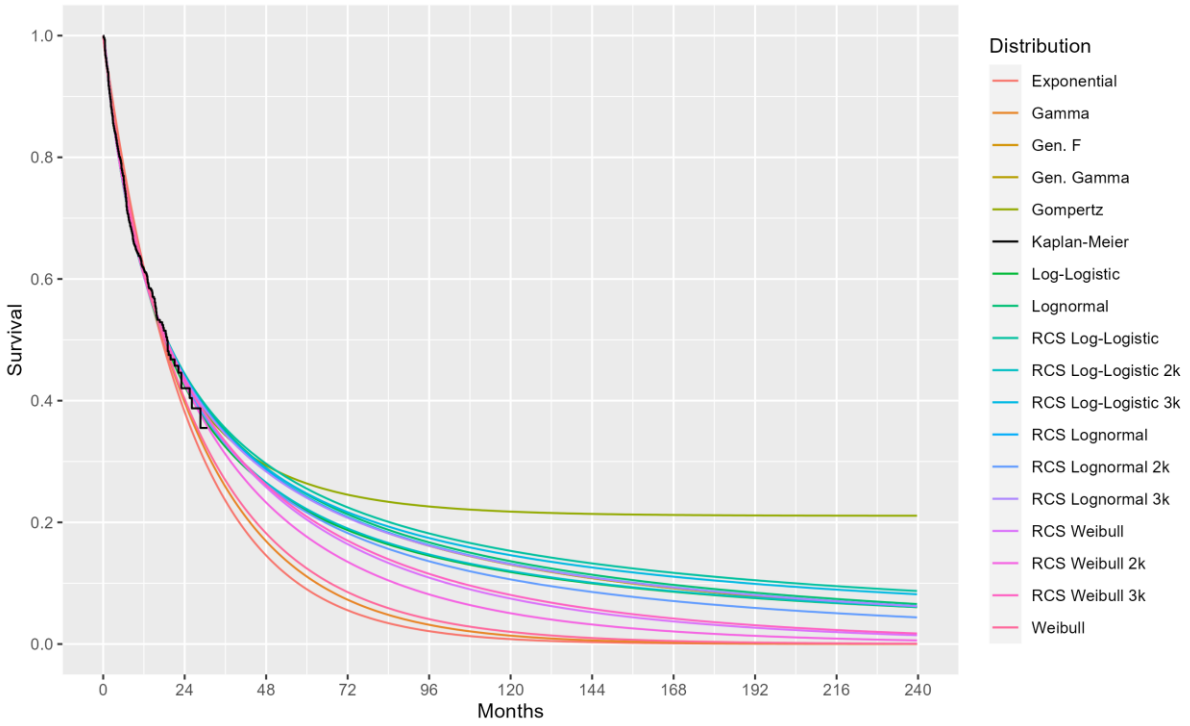
The EAG notes that although the lognormal model appears to provide the lowest AIC and BIC, other models such as generalised gamma, RCS lognormal, RCS Weibull 3k (3 knots) and RCS lognormal 2k (2 knots) have similar AIC scores which are all within 3 points difference, indicating equal goodness of fit comparing to the lognormal model. The EAG notes that RCS Weibull 3k appears to provide the best fit to the observed data. The company's base case lognormal model appears to overestimate the tail area of the KM curve (see Figure 16). Based on the above considerations, the EAG prefers the use of RCS Weibull 3k distribution to model OS for IsaPd in its base case.

Table 14: IsaPd OS independent model statistical goodness of fit (adapted from Table 44 in response to clarification question B13)

Distribution	AIC	AICc	BIC
Lognormal	2,591.50	2,591.50	2,600.70
Gen. Gamma	2,593.50	2,593.50	2,607.30
RCS Lognormal	2,593.50	2,593.50	2,607.30
RCS Weibull 3k	2,594.10	2,594.20	2,617.10
RCS Lognormal 2k	2,594.20	2,594.30	2,612.60
RCS Log-Logistic 3k	2,594.60	2,594.70	2,617.60
RCS Lognormal 3k	2,594.60	2,594.70	2,617.60
RCS Weibull	2,594.80	2,594.90	2,608.60
RCS Weibull 2k	2,595.10	2,595.20	2,613.50
RCS Log-Logistic 2k	2,595.30	2,595.40	2,613.70
Gen. F	2,595.50	2,595.60	2,613.90
RCS Log-Logistic	2,596.10	2,596.20	2,609.90
Log-Logistic	2,597.80	2,597.80	2,607.00
Gompertz	2,599.30	2,599.30	2,608.50
Weibull	2,604.90	2,604.90	2,614.10
Gamma	2,606.20	2,606.20	2,615.40
Exponential	2,606.90	2,606.90	2,611.50

2k – 2 knots; 3k – 3 knots; AIC – Akaike's Information Criterion; AICc – Akaike's Information Criterion Corrected; BIC – Bayesian Information Criterion; DF – degrees of freedom; IsaPd – isatuximab + pomalidomide + dexamethasone; OS – overall survival; RCS – restricted cubic splines

Figure 16: IsaPd OS, SACT, independently fitted to 20-year time horizon (reproduced from Figure 40 in response to clarification question B13)



2k – two knots; 3k – three knots; IsaPd – isatuximab + pomalidomide + dexamethasone; OS – overall survival; RCS – restricted cubic splines; SACT – systemic anti-cancer therapy

The company chooses the Weibull distribution as the base case to model daratumumab OS so that it aligns with the Evidence Review Group (ERG)'s preferred distribution for daratumumab SACT in TA783.[26] The BIC scores for the fits to OS provided within the CS are presented in Table 15. The plot of the fitted parametric models to the OS KM data are reproduced in Figure 17.

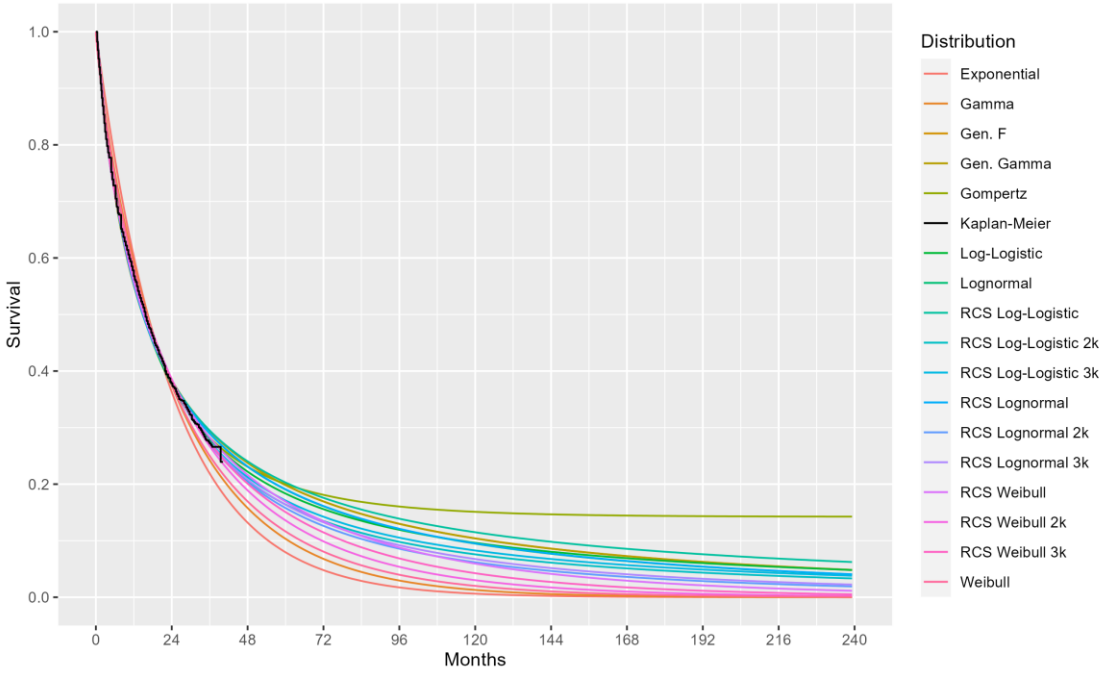
The EAG notes that the Weibull model provides much higher AIC and BIC scores compared with the RCS lognormal 3k and RCS lognormal 2k (the two models with the lowest AIC/BIC scores). The Weibull model also appears to underestimate the tail area of the KM curve (see Figure 17). The EAG also notes that the distribution chosen in TA783 was described by the ERG as conservative, which may be understandable as it was daratumumab monotherapy that was being appraised.[26] When daratumumab monotherapy was appraised there was the risk of recommending a treatment that was not ultimately cost-effective which could have influenced the ERG to select a conservative distribution; when it is a comparator, this risk does not exist and the best fitting distribution should be chosen. Based on the above considerations, the EAG prefers the use of RCS lognormal 2k distribution to model OS for daratumumab monotherapy in its base case.

Table 15: Daratumumab OS independent model statistical goodness of fit (adapted from Table 45 in response to clarification question B13)

Distribution	AIC	AICc	BIC
RCS Lognormal 3k	11,239.30	11,239.40	11,268.00
RCS Lognormal 2k	11,241.30	11,241.30	11,264.30
RCS Log-Logistic 3k	11,251.90	11,251.90	11,280.60
RCS Weibull 3k	11,253.60	11,253.60	11,282.30
RCS Log-Logistic 2k	11,257.20	11,257.20	11,280.10
RCS Weibull 2k	11,262.80	11,262.80	11,285.70
Lognormal	11,264.70	11,264.70	11,276.20
Gen. Gamma	11,265.90	11,265.90	11,283.20
RCS Lognormal	11,266.70	11,266.70	11,283.90
Gen. F	11,268.10	11,268.10	11,291.00
RCS Weibull	11,289.10	11,289.10	11,306.40
RCS Log-Logistic	11,298.10	11,298.10	11,315.30
Log-Logistic	11,305.50	11,305.50	11,316.90
Gompertz	11,316.30	11,316.30	11,327.80
Weibull	11,348.00	11,348.10	11,359.50
Gamma	11,361.00	11,361.00	11,372.50
Exponential	11,390.20	11,390.20	11,395.90

2k – 2 knots; 3k – 3 knots; AIC – Akaike's Information Criterion; AICc – Akaike's Information Criterion Corrected; BIC – Bayesian Information Criterion; DF – degrees of freedom; IsaPd – isatuximab + pomalidomide + dexamethasone; OS – overall survival; RCS – restricted cubic splines

Figure 17: Daratumumab OS, SACT, independently fitted to 20-year time horizon (reproduced from Figure 44 in response to clarification question B13)



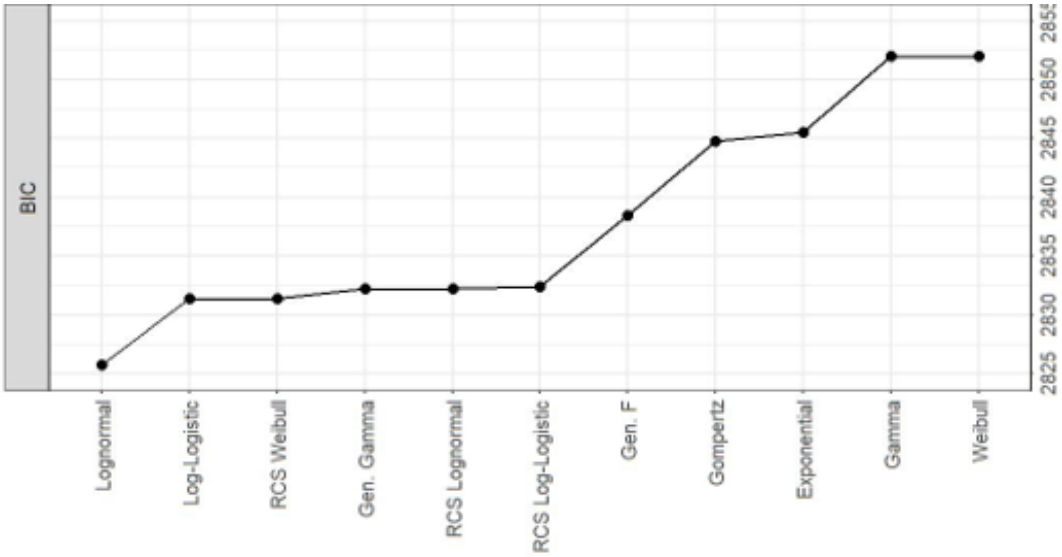
2k – two knots; 3k – three knots; IsaPd – isatuximab + pomalidomide + dexamethasone; OS – overall survival; RCS – restricted cubic splines; SACT – systemic anti-cancer therapy

4.2.4.3.2 Time to treatment discontinuation

The company chooses the lognormal distribution as the base case to model IsaPd TTD based on statistical (BIC) and visual fits. The company notes that there is no external data to validate the long-term prediction and that the lognormal distribution provides conservative results for the TTD for IsaPd. The BIC scores for the fits to TTD provided within the CS are presented in Figure 18. The plot of the fitted parametric models to the TTD KM data are reproduced in Figure 19.

The EAG agrees with the company's base case choice that the lognormal distribution appears to be the most appropriate model for TTD for IsaPd based on SACT data.

Figure 18: Bayesian Information Criteria fit to TTD data for the IsaPd SACT population (reproduced from Figure 22 of the CS Appendix R)



BIC – Bayesian Information Criterion; Gen. – generalised; IsaPd – isatuximab + pomalidomide + dexamethasone; SACT – systemic anti-cancer therapy; TTD – time-to-treatment discontinuation

Figure 19: Selected model fits to the TTD data for the IsaPd SACT population (reproduced from Figure 41 of the CS)

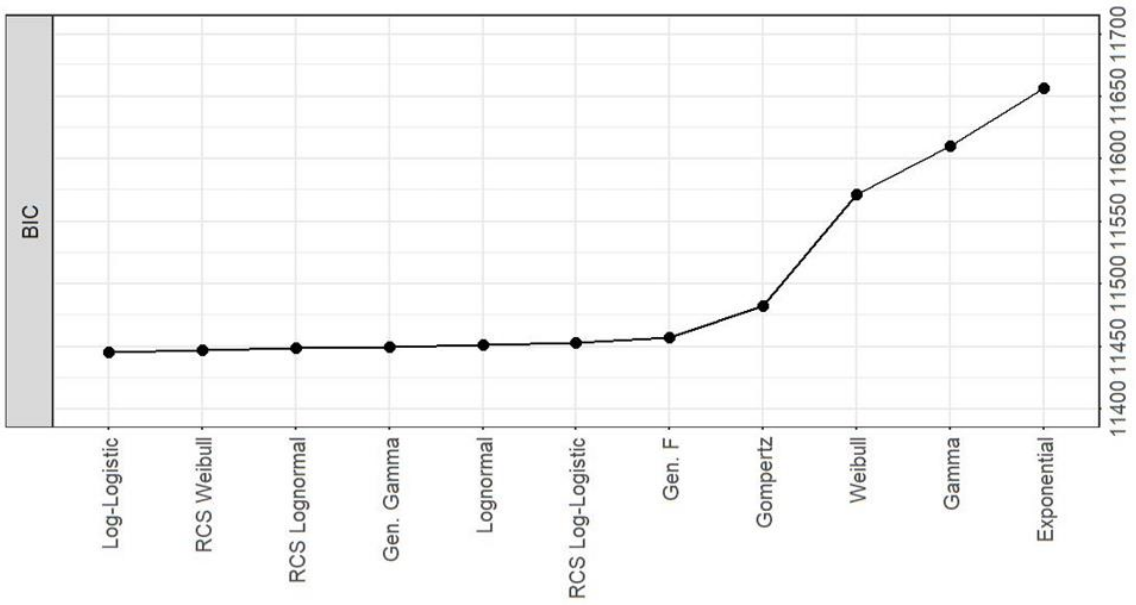
Gen. – generalised; IsaPd – isatuximab + pomalidomide + dexamethasone; RCS – restricted cubic splines; SACT – systemic anti-cancer therapy; TTD – time-to-treatment discontinuation

The company chooses the generalised gamma distribution as the base case to model TTD for daratumumab monotherapy to align with the ERG's preferred distribution for daratumumab SACT in TA783.[26] The BIC scores for the fits to TTD provided within the CS are presented in Figure 20. The plot of the fitted parametric models to the TTD KM data are reproduced in Figure 21.

The EAG notes that in TA783 the ERG's preferred model for daratumumab TTD SACT data was gamma instead of generalised gamma as the company stated in the CS. The gamma model provides a much higher BIC score compared with other models (see Figure 20).

The EAG agrees with the company's base case choice using the generalised gamma distribution to model the TTD SACT data as this distribution appears to have good statistical and visual fit.

Figure 20: Bayesian Information Criteria fit to TTD data for the daratumumab SACT population (reproduced from Figure 23 of the CS Appendix R)



BIC – Bayesian Information Criterion; Gen. – generalised; IsaPd – isatuximab + pomalidomide + dexamethasone; SACT – systemic anti-cancer therapy; TTD – time-to-treatment discontinuation

Figure 21: Selected model fits to the TTD data for the daratumumab SACT population (reproduced from Figure 41 of the CS)

[redacted]

Gen. – generalised; IsaPd – isatuximab + pomalidomide + dexamethasone; RCS – restricted cubic splines; SACT – systemic anti-cancer therapy; TTD – time-to-treatment discontinuation

4.2.4.4 *Description and critique of the company's survival analyses for IsaPd versus Pd (AFC)*

After factually inaccuracy check, the company submitted additional evidence using SACT data to inform the comparison between IsaPd and Pd. The detailed critique on using a naïve comparison based on this data can be found in Section 3.4.3. Only OS and TTD are available from SACT data and therefore the company assumes that PFS is equal to TTD which the EAG believes is a reasonable assumption.

For both OS and TTD, initially eight standard parametric models (exponential, Weibull, Gompertz, log-logistic, lognormal, gamma, generalised gamma, and generalised F distributions) and spline models with one/two/three knots (RCS lognormal, RCS Weibull and RCS log-logistic) were fitted independently to AFC Pd SACT data. The company used the same model for extrapolating IsaPd SACT data as described in Section 4.2.4.3.

4.2.4.4.1 Overall survival

The company states that "*With over three years of KM data available from Pd SACT, the survival extrapolation preferred by the clinicians and that most closely aligns with the available data is the RCS Weibull*". However, the company chooses the lognormal distribution as the base case to model Pd OS given that it had the best fit to the KM data and is associated with a conservative assumption for Pd. Fit statistics are presented in Table 16. The plot of the fitted parametric models to the OS KM data are reproduced in Figure 22.

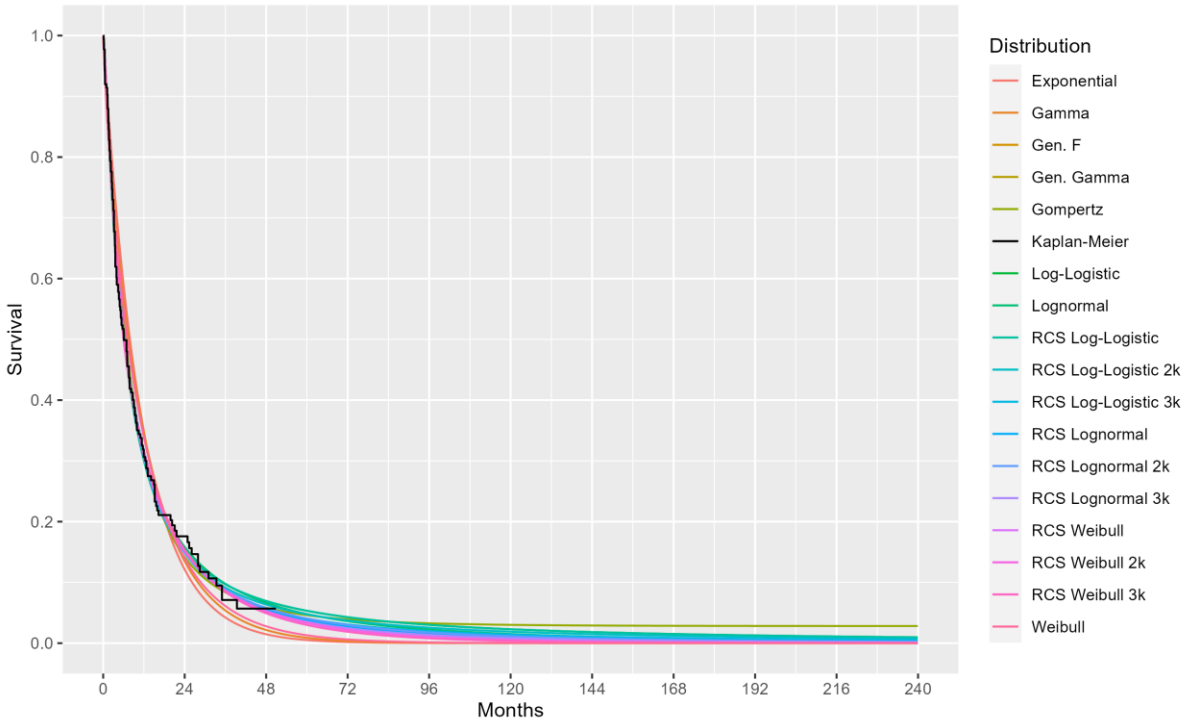
The EAG disagrees that the lognormal distribution provides the best fit to the KM data as it overestimates the data in the tail area. The EAG's preferred base case is the RCS Weibull with 1 knot as preferred by the company's clinicians.

Table 16: Pd OS independent model statistical goodness of fit (adapted from additional evidence Table 12)

Distribution	AIC	AICc	BIC
Lognormal	992.1	992.1	998.4
Log-Logistic	992.2	992.2	998.5
Gompertz	994.5	994.6	1,000.9
RCS Lognormal	993.0	993.2	1,002.5
RCS Weibull	993.0	993.1	1,002.5
Gen. Gamma	993.1	993.2	1,002.6
RCS Log-Logistic	994.2	994.3	1,003.7
Weibull	1,000.5	1,000.5	1,006.8
Exponential	1,004.0	1,004.0	1,007.1
RCS Lognormal 2k	994.9	995.1	1,007.5
Gen. F	995.1	995.3	1,007.7
RCS Weibull 2k	995.1	995.3	1,007.7
RCS Log-Logistic 2k	995.8	996.1	1,008.5
Gamma	1,003.0	1,003.0	1,009.3
RCS Lognormal 3k	995.9	996.2	1,011.7
RCS Weibull 3k	996.3	996.7	1,012.1
RCS Log-Logistic 3k	996.5	996.9	1,012.4

AIC - Akaike Information Criterion; AICc - corrected Akaike Information Criterion; BIC - Bayesian Information Criterion; Gen - generalise; k - knot; OS - overall survival; Pd - pomalidomide + dexamethasone; RCS - restricted cube spline.

Figure 22: Pd OS, SACT, independently fitted to 20-year time horizon (reproduced from additional evidence Figure 10)



Gen. - generalised; Pd - pomalidomide + dexamethasone; OS - overall survival; RCS -, restricted cubic splines; SACT - systemic anti-cancer therapy.

4.2.4.4.2 Time to treatment discontinuation

The company chooses the log-logistic distribution as the base case to model Pd TTD because it provides a more plausible long-term prediction while retaining reasonably good fit to the data. Fit statistics are presented in Table 17. The plot of the fitted parametric models to the TTD KM data is reproduced in Figure 23.

The EAG agrees with the company's base case choice that the log-logistic distribution appears to be the most appropriate model for TTD for AFC Pd SACT data.

Table 17: Pd TTD independent model statistical goodness of fit (adapted from additional evidence Table 11)

Distribution	AIC	AICc	BIC
Gompertz	799.1	799.2	805.5
Log-Logistic	799.3	799.4	805.7
Lognormal	803.5	803.6	809.8
RCS Log-Logistic	800.5	800.6	810.0
RCS Weibull	802.3	802.4	811.7
Gen. Gamma	805.3	805.4	814.8
RCS Lognormal	805.4	805.5	814.9
Gen. F	802.3	802.5	815.0
RCS Log-Logistic 2k	802.4	802.7	815.1
RCS Weibull 2k	802.9	803.1	815.6
RCS Lognormal 2k	804.2	804.4	816.8
RCS Weibull 3k	802.6	803.0	818.4
RCS Log-Logistic 3k	803.8	804.2	819.7
RCS Lognormal 3k	804.8	805.2	820.7
Weibull	833.1	833.2	839.5
Gamma	845.8	845.9	852.2
Exponential	857.7	857.7	860.9

AIC - Akaike Information Criterion; AICc - corrected Akaike Information Criterion; BIC - Bayesian Information Criterion; Gen - generalise; k - knot; OS - overall survival; Pd - pomalidomide + dexamethasone; RCS - restricted cube spline.

Figure 23: Pd TTD, SACT, independently fitted to 20-year time horizon (reproduced from additional evidence Figure 6)

Gen. - generalised; Pd - pomalidomide + dexamethasone; RCS - restricted cubic splines; SACT - systemic anti-cancer therapy; TTD- time to treatment discontinuation.

4.2.4.5 HRQoL

Health state utility values

HRQoL data used in the company's model is based on data collected in ICARIA-MM[9] using the EQ-5D-5L questionnaire. Within the study, the questionnaire was administered at day 1 of the first treatment course, and all subsequent treatment cycles (every 28 days) and at the 30 days after last treatment administration and during the post-treatment follow-up period (60±5 days after last treatment administration).[13]

Including those models fitted in the clarification process, the company fitted twelve GEE model to the available data accounting for repeated measures in the same patient. The twelve models (described in Table 34 of the CS for Models 1-6 and in Table 50 of the clarification response for Models 7-12) varied the covariates included from a list of: PFS by treatment arm; PPS; PFS on treatment, by treatment arm; PFS off treatment, by treatment arm; PPS on treatment; PPS off treatment; and whether the patient was within 12 weeks off death. The model selected by the company allowed a difference in PFS utility between IsaPd and Pd but used the same values for PPS and the terminal decrement. The rationale for this choice "*was used in the base case cost-effectiveness model as it aligned to the ERG and committee's preferred assumptions in the original appraisal for IsaPd [TA658]*". In the clarification response, the

goodness of fit of the twelve models were presented that showed that a model having covariates for only PFS and PPS was the best fitting model according to the quasi-likelihood information criterion.

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 Hernandez Alava *et al.*[35]

The utility estimates applied in the company's model are summarised in Table 18. 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. As the company could not identify utility data for patients being treated with daratumumab monotherapy are assumed to be the same as for Pd patients. The company justify this position by stating that "*these two treatments have similar PFS in clinical practice and are therefore likely to have a similar utility (HRQoL impact) for the PFS health state*"

Table 18: Mapped EQ-5D-3L estimates used in company's model

Health state	Mean utility and 95% CI†	
	IsaPd	Pd
Progression-free	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]
End-of life (terminal) decrement	[redacted]	[redacted]

† Underlying utility values for daratumumab monotherapy were assumed equal to IsaPd.

The model applies age-adjustment to the health state utilities based on UK general population norms reported by Hernandez Alava *et al*.[36]

The EAG notes that the utility values estimated from the ICARIA-MM study may not be applicable to the patients which form the SACT data set.

QALY losses due to AEs

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 (original CS, page 129).[2] In response to original clarification question B10[15] 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 EAG believes that this is reasonable although notes that in the company's clarification response[13] it appeared that the cycle length and therefore frequency of providing the EQ-5D-5L was 28 days rather than the 14 days previously stated.

For patients in the daratumumab group, the frequency of each AE considered was obtained from the company submission to NICE for daratumumab.[52] These frequencies were compared with the frequencies for Pd in the ICARIA-MM[9] to form a net change in the AEs. The disutilities associated with the AEs were estimated from a wide range of sources (see Section B.3.4.5) and durations of AEs were based on the company submission to NICE for daratumumab[52] and 28 days where the AE was not reported. The additional disutility that is associated with daratumumab monotherapy was estimated by the company to be [redacted] QALYs which was extracted from the company's mathematical model which was driven largely by an increased incidence of anaemia ([redacted]) associated with daratumumab monotherapy which was assumed to persist for 180 days in the base case with a disutility of 0.31.

4.2.4.6 Resource costs

This section provides a description of the resource costs included in the company's model and concludes with a summary table. Further details are provided in Section 3.5 of the CS.

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.

4.2.4.6.1 Acquisition and administration costs related to IsaPd, Pd and daratumumab monotherapy

Drug acquisition costs are modelled as a function of the mean body weight or BSA observed in ICARIA-MM,[9] the planned treatment schedule, RDI and unit costs. Based on its list price, the cost per pack of 100mg vial of isatuximab (1 days' supply) is £506.94. 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]. Drug prices were taken from the Electronic Market Information Tool (eMIT) for dexamethasone [45] and the BNF[46] for isatuximab, pomalidomide and daratumumab.

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 2020/2021 (codes SB11Z to SB14Z).[43]

Table 19 shows the assumed acquisition costs of isatuximab (with PAS applied), pomalidomide, dexamethasone and daratumumab. Following NICE guidance, only the PAS for isatuximab has been

incorporated with the list prices used for pomalidomide and daratumumab. The EAG notes that the administration costs of £281.11 for a subcutaneous injection appears high.

Table 19: The costs of interventions assumed in the company's base case along with administration costs

Treatment	Cost per pack (£)	Units per pack	Mg per unit	Administration costs (£) per administration
Daratumumab*	4320	1	1800	281.11
Dexamethasone	57.50	50	8	215.80†
Isatuximab	[redacted]	1	100	258.56 / 438.38††
Pomalidomide	8884.00	21	4	215.80†

**subcutaneous injection; † for first dose* only, thereafter zero †† the lower value for the first cycle, the higher value thereafter.

The company has assumed RDIs for the components of IsaPd and the components of Pd, based on an internal company analysis but has assumed that the RDI for daratumumab monotherapy is 100%. For IsaPd, isatuximab is assumed to have an RDI of [redacted], whilst pomalidomide has an RDI of [redacted] and dexamethasone has an RDI of [redacted]. For Pd the RDIs of pomalidomide and dexamethasone are assumed to be [redacted] and [redacted] respectively.

In the submission accompanying fact check[51], the company stated that it had undertaken "*separate calculations examining the cost difference when weight distribution vs. mean weight was used in isatuximab costing, it was found that using a weight distribution resulted in a [redacted] reduction in overall cost of isatuximab. This was implemented as a secondary discount after accounting for the PAS discount."* Whilst these calculations were not described the EAG has taken the reduction in isatuximab use at face value and has applied a discount of [redacted]% in the cost of isatuximab. The EAG has used this value within its base case.

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,[9] for daratumumab the proportions were taken from TA510 and TA783.[26, 50] These costs were [redacted] for patients receiving IsaPd ,[redacted] for patients receiving Pd, and [redacted] for patients receiving daratumumab monotherapy,

4.2.4.6.2 Disease management costs

Disease management costs are related to resource use for follow-up, and monitoring patients throughout their disease, such as medical visits, blood tests and biochemistry. The costs of disease management were assumed to be independent of both treatment and whether disease has progressed and was set as

£50.60 per week. Concomitant treatments included GCSF, red blood and platelet transfusions based on their usage in ICARIA-MM[9] for IsaPd and Pd and the company submissions relating to daratumumab. The costs of GCSFs was taken from TA510[50] inflated to 2022 costs.[49] The costs associated with red blood and platelet transfusions came from NHS Blood and DTS pricing.[53]

4.2.4.6.3 Costs of treatments following disease relapse / progression

The model includes the costs, both acquisition and administration, associated with treatments for relapse/progression after 4L treatment. Subsequent treatment use for IsaPd is taken from the SACT dataset for patients receiving IsaPd in the combined Early Access to Medicine Scheme or the CDF; subsequent treatments for Pd were assumed to be the same as for IsaPd. For daratumumab, subsequent therapy use is assumed to be that reported in TA783[26] using SACT data Only treatments that accounted for ≥2% of subsequent treatments were included with the remaining treatments reweighted. The subsequent treatments assumed in the model are shown in Table 20. Patients receiving IsaPd and Pd predominantly go on to receive bortezomib and panobinostat whereas patients on daratumumab monotherapy predominantly receive pomalidomide.

The costs of post-relapse/progression treatment use unit costs from the BNF, eMIT, and NHS Reference Costs 2021/2022. The average duration of treatment was estimated from external data (Kantar Health Study of treatments in RRMM in Western Europe).[47] The costs of subsequent treatments, weighted by the proportion of patients that received subsequent treatments, were assumed to be £31,417 for IsaPd and Pd and £66,120 for daratumumab monotherapy in the company's base case.

The EAG notes that the use of SACT data, rather than ICARIA-MM,[9] to inform subsequent treatments results in a loss of alignment between the interventions generating survival in ICARIA-MM and the costs of these interventions.

Table 20: The use of subsequent therapies assumed in the company's base case

Treatment	IsaPd / Pd	Dm	Cost in company's model
Belantamab mafodotin	6.2%	0.6%	£5707.83 per 100mg
Bendamustine	1.0%	2.1%	£82.89 for 5 * 100mg
Bendamustine and thalidomide	1.3%	1.2%	£82.89 for 5 * 100mg and £298.48 for 28* 50mg
Bortezomib	1.3%	0.8%	£762.38 per 3.5mg
Bortezomib and panobinostat	19.4%	16.7%	£762.38 per 3.5mg and £4656.00 for 6 * 20mg
Cyclophosphamide	3.6%	2.8%	£8.33 per 500mg
Cyclophosphamide and pomalidomide	0.3%	4.6%	£8.33 per 500mg and £8884.00 for 21 * 4mg
Cyclophosphamide and thalidomide	1.3%	1.1%	£8.33 per 500mg and £298.48 for 28* 50mg
Melphalan	3.3%	2.3%	£30.93 for 25 * 2mg
Pomalidomide	0.7%	49.9%	£8884.00 for 21 * 4mg

Dm – daratumumab monotherapy; IsaPd – isatuximab, pomalidomide and dexamethasone; Pd - pomalidomide and dexamethasone

4.2.4.6.4 Costs of managing AEs

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 2020/21.[43] The frequency of events for IsaPd and Pd were obtained from data for 4L patients in the ICARIA-MM study,[9] whilst the probabilities of having any of the AEs for daratumumab were obtained from the company's submission to NICE for daratumumab's appraisal by NICE.[52] The frequencies of AE per intervention, the unit costs of each AE and the estimated costs of AEs for each intervention are presented in Table 21. The EAG notes that AEs associated with IsaPd can change depending on the scenario as the company intended to only use AEs where one intervention had a value of 5% or greater. However, some AEs (hypokalaemia and nausea) were considered despite all values being below 5%. The EAG believes this will have minimal input on the ICER.

Table 21: Frequency, unit costs and total costs associated with Grade ≥3 AEs

Adverse event	Frequency of AEs (IsaPd versus Pd)		Frequency of AEs (IsaPd versus Dm)		Unit costs (£)
	IsaPd	Pd	IsaPd	Dm	
Acute kidney injury	3.8%	5.2%	0.0%	0.0%	4876
Anaemia	0.0%	0.0%	0.0%	13.1%	800
Fatigue	5.8%	0.0%	5.8%	0.8%	774
Febrile neutropenia	13.5%	6.9%	13.5%	1.2%	7126
Hypercalcaemia	1.9%	5.2%	0.0%	0.0%	4002
Hypokalaemia	0.0%	0.0%	0.0%	0.4%	732
Lower respiratory tract infection	7.7%	0.0%	7.7%	1.5%	1858
Lymphopenia	0.0%	0.0%	0.0%	5.0%	928
Nausea	0.0%	0.0%	0.0%	0.4%	774
Neutropenia	46.2%	32.8%	46.2%	13.1%	928
Pneumonia	21.2%	24.1%	21.2%	2.7%	845
Thrombocytopenia	9.6%	10.3%	9.6%	13.8%	1151
Total costs (£)	**2129**	**1578**	**1864**	**577**	

IsaPd – isatuximab in combination with pomalidomide and dexamethasone; Pd – pomalidomide and dexamethasone; Dm – daratumumab monotherapy

4.2.4.6.5 Costs of end-of-life care

Costs related to terminal care were based on the pomalidomide submission to NICE (TA427),[48] updated to 2022 costs.[49] These costs, appropriately discounted, are applied in the cycle in which a patient died and are assumed to incorporate hospital, hospice, and home services, prior to death.

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,[9] for daratumumab the proportions were taken from TA510 and TA783.[29, 53]

Table 22: Summary of costs applied in the company's model

Cost parameter	Base case analysis (£)		Exploratory analysis (£)	
	IsaPd §	Pd	IsaPd§	Dm
Drug costs per initial cycles*	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs (per week, initial cycles*)	[redacted]	[redacted]	[redacted]	[redacted]
Drug costs per cycle (after the initial cycles*)	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs (per week, after the initial cycles*)	[redacted]	[redacted]	[redacted]	[redacted]
Disease management – event-free (per week)	50.60	50.60	50.60	50.60
Disease management – progressed disease (per week)	50.60	50.60	50.60	50.60
Disease management – concomitant treatments (once-only)	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment drug and administration costs (post-progression, once-only, applied to discontinuers in each cycle)	[redacted]	[redacted]	[redacted]	[redacted]
End of life care (once-only)	981.41	981.41	981.41	981.41
Grade 3+ AEs (once-only)	2129.06	1577.63	1864.58	577.01

AE - adverse event; Dm – daratumumab monotherapy IsaPd – isatuximab in combination with pomalidomide and dexamethasone; PanVd - panobinostat, with bortezomib and dexamethasone; Pd – pomalidomide and dexamethasone.
*Notes: * The initial cycles are the first cycles for IsaPd and PD and the first two cycles for daratumumab monotherapy. † the lower cost is applied after 24 weeks*
§Includes PAS for isatuximab.

4.2.5 Model evaluation methods

The CS base case presents ICERs for IsaPd versus Pd and for IsaPd versus daratumumab monotherapy. Results are presented using the deterministic and probabilistic versions of the model. The probabilistic ICERs are based on 1,000 Monte Carlo simulations. Sampled values were generated by the company used one of the following: modified 95% confidence intervals; bootstrapped data from the ICARIA-MM study or an assumption that standard errors were assumed to be 25% of the mean, logged where appropriate. The results of the PSA were presented in the CS 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.

4.2.6 Company's model validation and verification

Section B.3.12 of the CS describes the company's validation activities performed by the model developers and by two health economists not involved in the development of the model which included: cell-by-cell checks of formula; rebuilding of key sections of the model; logical tests; and a full audit of

model inputs. The company states that four experienced UK haematologists were involved in forming a "*consensus 'group weighting'*" of the OS survival distributions although the experts were only shown jointly-fitted models (Question B14 of the company's response to clarification).[13]

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. This section is divided into two subsections relating to the company's comparison of IsaPd against Pd and the company's comparison of IsaPd against daratumumab monotherapy. As requested by NICE, the results generated by the company have incorporated the PAS associated with isatuximab but not PASs associated with any other drug.

The company has provided in Section 3.8.3 of the CS a narrative on why combination therapy should potentially be considered using a different methodology than single treatments, although this is not permitted within NICE's reference case.[54] The company provided an analysis to show the costs and QALYs attributable to isatuximab within the IsaPd combination and provided further analyses to indicate the percentage of total medication costs for each component of IsaPd under different cost assumptions for each component. As these analyses are not aligned with NICE's reference case the EAG has not discussed these further.

4.2.7.1 Company's model results comparing IsaPd to Pd

4.2.7.1.1 Base case results using data from ICARIA-MM

Table 23 presents the central estimates of cost-effectiveness generated using the company's model for the comparison of IsaPd versus Pd. The company has also provided many analyses which do not meet NICE's reference case,[54] which include removing the costs of pomalidomide and dexamethasone or assuming that generic pomalidomide is available, but which are not discussed further by the EAG.

The probabilistic version of the model estimates that IsaPd generates an additional [redacted] QALYs per patient compared to Pd at an additional cost of [redacted] resulting in an ICER of £192,673 per QALY gained. The deterministic version of the model produces a lower ICER of £182,769 per QALY gained.

Table 23: Company's base case results - IsaPd versus Pd (discounted values)

Option	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. Costs (£)	ICER (£)
Probabilistic model							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**192,673**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic model							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**182,769**
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; N/R – not reported Pd – pomalidomide and dexamethasone

The scatter plot provided by the company showed that all PSA iterations resulted in an ICER greater than £50,000 per QALY. The CEAC presented in the company's model suggested that the probability of IsaPd having an ICER below £100,000 was [redacted]%. None of the deterministic analyses provided in the updated tornado diagram had a ICER below [redacted] within the model (not provided in the documents supplied by the company although originally in Figure 49 in the CS). None of the deterministic scenario analyses provided by the company had a ICER below [redacted] within the model (not provided in the documents supplied by the company although originally in Table 69 in the CS) with the most impactful in reducing the ICER being the assumption that there was no wastage of medication.

4.2.7.1.2 Base case results AFC

Table 24 presents the central estimates of cost-effectiveness for IsaPd versus Pd in the company's base case AFC. The company has also provided many analyses which do not meet NICE's reference case,[54] which include removing the costs of pomalidomide and dexamethasone or assuming that generic pomalidomide is available, but which are not discussed further by the EAG.

The probabilistic version of the model estimates that IsaPd generates an additional [redacted] QALYs per patient compared to Pd at an additional cost of [redacted] resulting in an ICER of £125,932 per QALY gained. The deterministic version of the model produces a slightly lower ICER of £124,744 per QALY gained.

Table 24: Company's base case results AFC- IsaPd versus Pd (discounted values)

Option	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. Costs (£)	ICER (£)
Probabilistic model							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**125,932**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic model							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**124,744**
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; N/R – not reported Pd – pomalidomide and dexamethasone

The scatter plot provided by the company showed that all PSA iterations resulted in an ICER greater than £50,000 per QALY. The CEAC presented in the company's model suggested that the probability of IsaPd having an ICER below £100,000 was [redacted]%. None of the deterministic analyses provided in the updated tornado diagram had a ICER below [redacted] within the model. None of the deterministic scenario analyses provided by the company had a ICER below [redacted] within the model with the most impactful in reducing the ICER being the assumption that there was no wastage of medication.

4.2.7.2 Company's model results comparing IsaPd to daratumumab monotherapy

Table 25 presents the central estimates of cost-effectiveness generated using the company's model for the comparison of IsaPd versus daratumumab monotherapy. The company has also provided many analyses which do not meet NICE's reference case,[54] which include removing the costs of pomalidomide and dexamethasone or assuming that generic pomalidomide is available, but which are not discussed further by the EAG.

The probabilistic version of the model estimates that IsaPd generates an additional [redacted] QALYs per patient compared to pomalidomide with dexamethasone at an additional cost of [redacted] resulting in an ICER of £142,577 per QALY gained. The deterministic version of the model produces a higher ICER of £144,981 per QALY gained.

Table 25: Company's base case results - IsaPd versus daratumumab monotherapy (discounted values)

Option	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. Costs (£)	ICER (£)
Probabilistic model							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£142,577**
Dm	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic model							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£144,981**
Dm	[redacted]	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year Dm – daratumumab monotherapy; IsaPd – isatuximab in combination with pomalidomide and dexamethasone; N/R – not reported

The scatter plot provided by the company showed that all PSA iterations resulted in an ICER greater than £50,000 per QALY. The CEAC presented in the company's model suggested that the probability of IsaPd having an ICER below £100,000 was [redacted]%. None of the deterministic analyses provided in the updated tornado diagram had a ICER below [redacted] within the model (not provided in the documents supplied by the company although originally in Figure 50 in the CS). None of the deterministic scenario analyses provided by the company had a ICER below [redacted] within the model (not provided in the documents supplied by the company although originally in Table 70 in the CS) with the most impactful in reducing the ICER being the assumption that there was no wastage of medication.

4.3 Critical appraisal of the company's health economic analysis

The EAG 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:

- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the EAG.
- Examination of the correspondence between the description of the model reported in the CS[2] and the company's executable model.
- 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 26). Each element is discussed in further detail within the EAG report.

Table 26: Adherence of the company's economic analyses to the NICE Reference Case

Element	Reference case	EAG 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;[8] except that the population within the company's base case is narrower than specified within the scope (restricted to those at 4L).
Comparator(s)	As listed in the scope developed by NICE	The NICE scope[8] specifies multiple comparators. The company's base case focusses on Pd as the comparator but performed an exploratory analysis comparing IsaPd with daratumumab monotherapy. The company provided rationales as to why other comparators were not included that satisfied the EAG.
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 full incremental analysis	The results of the analyses are presented in terms of the incremental cost per QALY gained. The company has also chosen to present results in terms of cost per life years gained. Due to the differences sources used in the comparisons (ICARIA-MM for the comparison with Pd and SACT data for the comparison with daratumumab) a full incremental analysis was not undertaken with only pairwise ICERs presented.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 40-year time horizon which was assumed to equate to a patient's lifetime.
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; this was the key study included in the company's systematic review of clinical evidence. For the comparison with daratumumab data time-to-event outcomes (TTD and OS) were estimated based on digitised SACT data.
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[9] recorded EQ-5D-5L values which were mapped to EQ-5D-3L values.[35] A GEE regression model was fitted to the EQ-5D-3L data. The company assumed that the HRQoL data for daratumumab would equal that of Pd in the progression-free, and the progressed health states.

Element	Reference case	EAG comments
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 explicitly applied to estimated QALY gains in the company's base case. However, the company makes the claim that "*IsaPd should continue to be assessed at a cost-effectiveness threshold of £50,000/QALY, due to the process inequity for this appraisal, as expected at entry into CDF and the severe nature of RRMM at 4th line."*
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 generally valued at 2020/21 prices with drug costs set at 2022 or 2023 prices.

AE - adverse event; CS - company's submission; EFS - event-free survival; EAG - 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; SACT – systemic anti-cancer treatment

4.3.2 Main issues identified within the critical appraisal

In general, the EAG believed the revised model structure and the parameter values used were appropriate for the decision problem. However, some limitations were identified by the EAG which make notable changes to the ICER. Box 1 summarises these main issues which are discussed in further detail in the subsequent sections. Limitations identified that were thought to change the ICER only marginally are not discussed.

Box 1: Main issues identified within the critical appraisal undertaken by the EAG

(1) A perceived error identified within the company's model
(2) Use of jointly-fitted survival models means that a treatment effect is assumed in perpetuity for OS even in patients who have progressed
(3) The EAG believes that independently-fitted lognormal distributions are more appropriate to model PFS in the IsaPd versus Pd comparison
(4) The modelling of subsequent treatments costs and OS
(5) The EAG believes that alternative distributions are more appropriate to model OS in the IsaPd versus daratumumab monotherapy comparison
(6) Uncertainty associated with the most appropriate utility estimates used within the model for IsaPd, Pd and daratumumab monotherapy
(7) The administration costs associated with daratumumab monotherapy appear high
(8) Use of a distribution for weight should be within the base case
(9) Reliance on a naïve indirect comparison for IsaPd and daratumumab monotherapy
(10) Reliance on a naïve indirect comparison for IsaPd and Pd in the company's base case AFC
(11) The EAG believes that alternative distributions are more appropriate to model OS in the IsaPd versus Pd comparison in the company's base case AFC

4.3.2.1 A perceived error identified within the company's model

During the FACT Check process the EAG identified a perceived error that had not previously been noted (and corrected by the company) which had a large impact on the ICER. The perceived error was a misspecification of a reference within cell FX26 of the 'Comp1Calc' worksheet that used 'comp1.pp_tx10' twice rather than using 'comp1.pp_tx11' in the second usage. In the 'Comp2Calc' and 'Comp4Calc' worksheets this problem was not apparent with both 'comp2.pp_tx11' and 'comp4.pp_tx11' being correctly used. The EAG amended the erroneous cell to use 'comp1.pp_tx11' instead of the second usage of 'comp1.pp_tx10'.

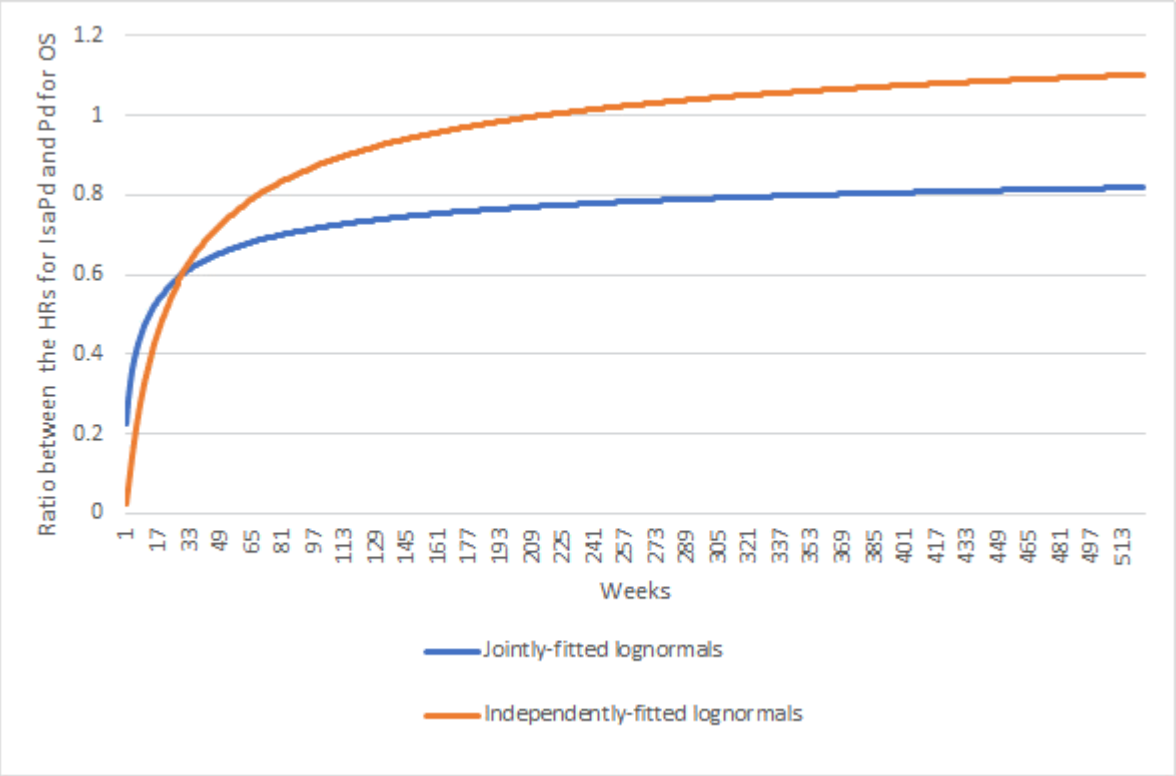
4.3.2.2 Use of jointly-fitted survival models means that a treatment effect is assumed in perpetuity for OS even in patients who have progressed

The company has assumed jointly-fitted survival models for OS. Figure 24 shows the HR of OS over the first 10-year period for IsaPd compared with Pd. This shows that the use of the company's jointly-fitted lognormal survival model for OS means that IsaPd is forever associated with a benefit in MM-related death compared with Pd even though a large proportion of patients have progressed (which is in the region of 80% at 5 years for people receiving IsaPd). The EAG believes that maintaining an OS benefit many years after progression is unlikely to be plausible.

The EAG has also plotted the HR between IsaPd and Pd when using independently-fitted lognormal distributions in Figure 24. The EAG notes that after 4 years these models predict that the risk of death was greater for those who had received IsaPd than for those that received Pd (as the HR is above unity). This was deemed unlikely to be plausible to the EAG.

The EAG has assumed in its base case that independently-fitted lognormal distributions would be used until the HR exceeds unity, at which point unity was used. The EAG has also run analyses for OS using the company's preferred jointly-fitted lognormal distributions and exponential distributions. In the CS it is stated that "*Clinical opinion of four highly experienced UK haematologists suggested that the jointly fitted exponential distribution was likely to better represent expected long-term survival in patients receiving treatment at 4th line in UK clinical practice*".

Figure 24: Displaying the ratios of the HRs for IsaPd and Pd for OS when using jointly-fitted and when using independently-fitted survival models



4.3.2.3 The EAG believes that independently-fitted lognormal distributions are more appropriate to model PFS for the IsaPd versus Pd comparison

As described in Section 4.2.4.2.2 the EAG preferred the use of independently-fitted lognormal distributions to the jointly-fitted RCS Weibull distributions used by the company. The EAG used independently-fitted lognormal distributions in its base case but used the company's jointly-fitted RCS Weibull distributions in a scenario analysis.

For PFS, the EAG found it plausible that there would be an ongoing advantage for IsaPd over Pd which differed from the view for OS when patients had progressed on IsaPd treatment.

4.3.2.4 The modelling of subsequent treatments costs and OS

The observed survival data which are used to inform the survival distributions comparing IsaPd with Pd are associated with a set of subsequent treatments that are different to those costed by the company. The survival distributions used in the comparison of IsaPd and Pd have been taken from the ICARIA-MM study. In this study subsequent treatments were provided that are not routine treatment in the UK, however, these treatments may have been providing additional benefits above that which would be received by standard UK practice. In order to align the costs and benefits of subsequent

treatments the EAG has used the costs associated with the subsequent treatments in ICARIA-MM in its base case.

The distributions of subsequent treatment used in the EAG base case in the IsaPd and Pd comparison is shown in Table 27; these data are taken from ICARIA-MM. The costs are those shown in Table 20 except for carfilzomib, which was not included in the company's base case.

Table 27: The use of subsequent therapies assumed in the EAG's base case

Treatment	IsaPd	Pd	Cost in the company's model
Belantamab mafodotin	[redacted]	[redacted]	£5707.83 per 100mg
Bendamustine	[redacted]	[redacted]	£82.89 for 5 * 100mg
Bortezomib	[redacted]	[redacted]	£762.38 per 3.5mg
Carfilzomib	[redacted]	[redacted]	£1056.00 per 100mg
Cyclophosphamide	[redacted]	[redacted]	£8.33 per 500mg
Daratumumab	[redacted]	[redacted]	£1440 per 400mg
Doxoribicin	[redacted]	[redacted]	£234.66 per 200mg
Etoposide	[redacted]	[redacted]	£11.50 per 100mg
Lenalidomide	[redacted]	[redacted]	£4368.00 for 21 * 25mg
Melphalan	[redacted]	[redacted]	£30.93 for 25 * 2mg
Pomalidomide	[redacted]	[redacted]	£8884.00 for 21 * 4mg

IsaPd – isatuximab, pomalidomide and dexamethasone; Pd - pomalidomide and dexamethasone

The company only explored the impact of subsequent therapies by using the TSE-adjusted HR to account for subsequent daratumumab therapy, where the TSE-adjusted HR is associated with a more favourable HR for IsaPd versus Pd compared to the IPCW-adjusted HR. The estimated OS after applying the TSE-adjusted HR lacks face validity as the estimated survival for Pd does not appear to change and the estimated survival for IsaPd is more favourable than before the adjustment. The EAG would have anticipated that the survival estimates for both IsaPd and Pd would have been less favourable after removing daratumumab at 5th line. Hence, the EAG's base case model uses the OS data from the ICARIA-MM study without adjustment.

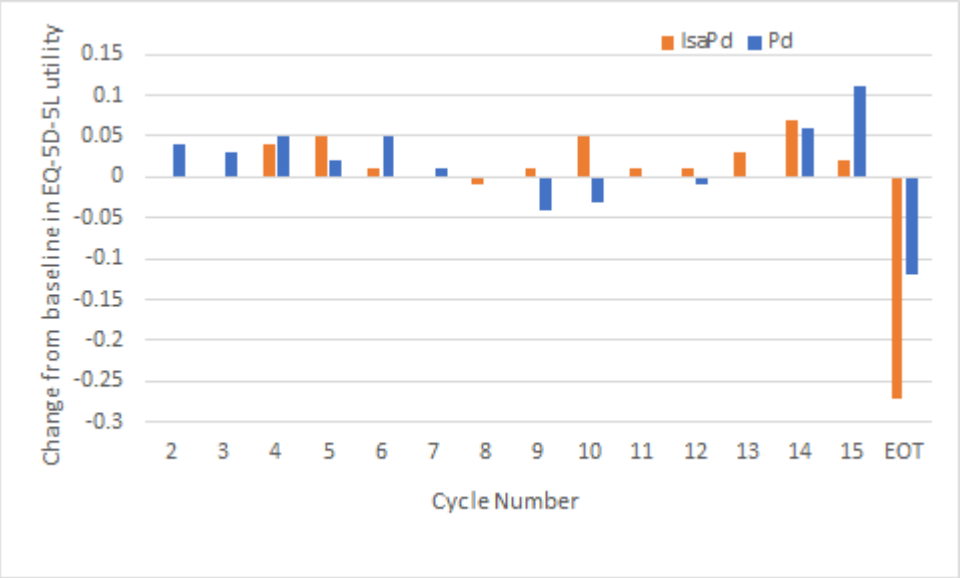
4.3.2.5 The EAG believes that alternative distributions are more appropriate to model OS in the IsaPd versus daratumumab monotherapy comparison

As described in Section 4.2.4.3.1, the EAG preferred the use of an RCS Weibull 3k distribution to model OS for IsaPd and the use of an RCS lognormal 2k distribution to model OS for daratumumab monotherapy. Scenario analyses were run using the company's preferred choice of lognormal and Weibull distributions for IsaPd and daratumumab monotherapy respectively.

4.3.2.6 Uncertainty associated with the most appropriate utility estimates used within the model for IsaPd, Pd and daratumumab monotherapy

The company choose a model that incorporated differential treatment utility in PFS by treatment arm for IsaPd and Pd and a decrement for approaching death. The EAG has maintained this in its base case as it was previously the Appraisal Committee's preferred assumption and clinical advisors to the EAG suggested that IsaPd produces a better depth of remission than Pd and would have better control of symptoms. However, a simpler model that used the same utility regardless of treatment arm may be plausible as it produced a better fit, and the data provided on utility change from baseline for IsaPd and Pd (Table 13 of the company's response to clarification) provides no clear indication that IsaPd produced more of a benefit than Pd (as shown in Figure 25). This simpler model where the utility in PFS was independent of treatment was used in a sensitivity analysis.

Figure 25: Change from baseline in EQ-5D-5L utility by treatment arm and cycle number or end of treatment



For the comparison of IsaPd with daratumumab monotherapy the EAG maintained the company's assumption that daratumumab monotherapy had the same utility as Pd as clinical advice provided to the EAG suggested that the depth of remission for daratumumab monotherapy was closer to that of Pd than IsaPd. The EAG sets the utility for daratumumab monotherapy to that of IsaPd in a sensitivity analysis.

4.3.2.7 The administration costs associated with daratumumab monotherapy appear high

As described in Section 4.2.4.6.1 the company has assumed an administration cost of £281.11 for every subcutaneous injection of daratumumab monotherapy. The EAG has run an analysis where this cost is applied for the first dose only with no further costs incurred in subsequent cycles.

4.3.2.8 Use of a distribution for weight should be within the base case

As described in Section 4.2.4.6.1, at fact check, the company described additional analyses that used the distribution of weight rather than using the mean value for all patients. This is more appropriate, and results in a decrease in the costs of isatuximab which has weight-based dosing. The EAG has incorporated this reduction into its base case.

4.3.2.9 Reliance on a naïve indirect comparison for IsaPd and daratumumab monotherapy

As described in Section 4.2.4.3 the company compared IsaPd and daratumumab monotherapy using a naïve indirect comparison. As acknowledged by the company such comparisons are prone to bias so the results should be treated with caution which the EAG concurs with.

4.3.2.10 Reliance on a naïve indirect comparison for IsaPd and Pd in the company's base case AFC

As described in Section 4.2.4.4, the company compared IsaPd and Pd using a naïve indirect comparison of AFC Pd SACT and IsaPd SACT. The EAG believes that this analysis is prone to bias as the population for Pd may be less healthy than the population for IsaPd and no adjustments were conducted for potential confounders. The EAG also believes that the relative treatment effect of IsaPd versus Pd would be better informed by the head-to-head RCT (ICARIA-MM).

4.3.2.11 The EAG believes that alternative distributions are more appropriate to model OS when using SACT data for Pd in the company's base case AFC

As described in Section 4.2.4.3.1, the EAG preferred the use of an RCS Weibull 3k distribution to model OS for IsaPd. As described in Section 4.2.4.4.1, the EAG preferred the use of an RCS Weibull with 1 knot. Scenario analyses were run using the company's preferred choice of lognormal distributions for both IsaPd and Pd.

4.4 EAG's exploratory analyses

This section presents the methods and results of the EAG's exploratory analyses undertaken using the company's model.

4.4.1 Overview of the EAG's exploratory analyses

The EAG undertook exploratory analyses to address the key points identified within the critical appraisal (Section 4.3.3). Combinations of these exploratory analyses formed the EAG's base case analysis. The EAG also undertook additional sensitivity analyses using the EAG's base case model to explore the impact of alternative assumptions on the ICER. The EAG could not explore uncertainty generated by the naïve indirect comparison of IsaPd and daratumumab monotherapy but highlights that this uncertainty exists.

4.4.2 EAG exploratory analysis – methods

4.4.2.1 EAG base case analysis for IsaPd compared with Pd

4.4.2.1.1 Base case results using data from ICARIA-MM

The EAG's base case analysis is comprised of three amendments to the company's model: EAG exploratory analysis 1, 2, 3, 4 and 5; these are detailed below.

EAG exploratory analysis 1: Amending the perceived error within the company's model

The EAG made the amendment detailed in Section 4.3.2.1

EAG exploratory analysis 2: The use of independently-fitted lognormal distributions to model OS but ensuring that the risk of death was never higher in the IsaPd arm than the Pd arm

The EAG changed the distributions for OS to be independently-fitted lognormals but ensured that the hazard of death in the IsaPd arm was never greater than in the Pd arm.

EAG exploratory analysis 3: The use of independently-fitted lognormal distributions to model PFS

The EAG changed the distributions for PFS to be independently-fitted lognormals.

EAG exploratory analysis 4: Using the costs of subsequent treatments associated with ICARIA-MM

The EAG has used the costs associated with the treatments provided in ICARIA-MM to align with the observed survival data.

EAG exploratory analysis 5: Using the distribution of weight for patients rather than using the mean weight

The EAG has increased the PAS discount to take into consideration the fact that patients have a distribution of weights rather than all having the mean value. See Section 4.2.4.6.1 for further details.

Additional sensitivity analyses undertaken on the EAG base case for IsaPd versus Pd

The following additional sensitivity analyses were undertaken using the EAG's base case.

EAG additional sensitivity analysis 1: Use of alternative models for OS

The EAG assessed the impact on the ICER when the company's preferred choice (jointly-fitted lognormal distributions) was used to model OS and when exponential distributions were used to model OS.

EAG additional sensitivity analysis 2: Use of alternative models for PFS

The EAG assessed the impact on the ICER when the company's preferred choice (jointly-fitted RCS Weibull distributions) was used to model PFS.

EAG additional sensitivity analysis 3: Use of alternative models for estimating HRQoL

The EAG assessed the impact on the ICER when using the company's Model 8 for determining HRQoL, which assumed treatment independent values for PFS utility. The resulted in the utility for PFS changing from [redacted] for IsaPd and [redacted] for Pd to a value of [redacted] for both treatments. The decrement associated with death changed from [redacted] to [redacted].

4.4.2.1.2 Base case results AFC

The EAG's base case analysis is comprised of two amendments to the company's model: exploratory analyses 6, 7 and 8.

EAG exploratory analysis 6: Amending the perceived error within the company's model

The EAG made the amendment detailed in Section 4.3.2.1

EAG exploratory analysis 7: Alternative distributions for OS

The EAG changed the distributions for OS to be an RCS Weibull with 3 knots for IsaPd and an RCS Weibull with 1 knot for Pd.

EAG exploratory analysis 8: Using the distribution of weight for patients rather than using the mean weight

The EAG has increased the PAS discount to take into consideration the fact that patients have a distribution of weights rather than all having the mean value. See Section 4.2.4.6.1 for further details.

Additional sensitivity analyses undertaken on the EAG base case for IsaPd versus Pd AFC

Two additional sensitivity analyses were undertaken using the EAG's base case.

EAG additional sensitivity analysis 4: Use of alternative models for OS

The EAG assessed the impact on the ICER when the company's preferred choice (lognormal distributions for both IsaPd and Pd) were used to model OS.

EAG additional sensitivity analysis 5: Use of alternative models for estimating HRQoL

The EAG assessed the impact on the ICER when using the company's Model 8 for determining HRQoL, which assumed treatment independent values for PFS utility. The resulted in the utility for PFS changing from [redacted] for IsaPd and [redacted] for Pd to a value of [redacted] for both treatments. The decrement associated with death changed from [redacted] to [redacted].

4.4.2.2 EAG base case analysis for IsaPd compared with daratumumab monotherapy

The EAG's base case analysis is comprised of three amendments to the company's model EAG exploratory analyses 9, 10, 11 and 12; these are detailed below.

EAG exploratory analysis 9: Amending the perceived error within the company's model

The EAG made the amendment detailed in Section 4.3.2.1

EAG exploratory analysis 10: Alternative distributions for OS

The EAG changed the distributions for OS to be an RCS Weibull with 3 knots for IsaPd and an RCS lognormal with 2 knots for daratumumab monotherapy.

EAG exploratory analysis 11: Reducing the administration costs associated with subcutaneous injections

The EAG set the administration costs of subcutaneous injections to zero after the first dose but maintained the value of £281.11 for the first dose.

EAG exploratory analysis 12: Using the distribution of weight for patients rather than using the mean weight

The EAG has increased the PAS discount to take into consideration the fact that patients have a distribution of weights rather than all having the mean value. See Section 4.2.4.6.1 for further details.

Additional sensitivity analyses undertaken on the EAG base case for IsaPd versus daratumumab monotherapy

Two additional sensitivity analyses were undertaken using the EAG's base case.

EAG additional sensitivity analysis 6: Use of alternative models for OS

The EAG assessed the impact on the ICER when the company's preferred choice (a lognormal distribution for IsaPd and a Weibull distribution for daratumumab monotherapy) were used to model OS.

EAG additional sensitivity analysis 7: Use of alternative models for estimating HRQoL

The EAG assessed the impact on the ICER when using the company's Model 8 for determining HRQoL, which assumed treatment independent values for PFS utility. The resulted in the utility for PFS changing from [redacted] for IsaPd and [redacted] for daratumumab monotherapy to a value of [redacted] for both treatments. The decrement associated with death changed from [redacted] to [redacted].

4.4.3 EAG exploratory analysis – results

4.4.3.1 *IsaPd versus Pd*

4.4.3.1.1 EAG exploratory analyses using data from ICARIA-MM

EAG base case analysis results

Table 28 presents the results of the EAG's preferred analysis. As shown in the table, four changes increase the ICER with the most impactful being the change in distributions used for OS which produced a change from £182,769 to £248,450 per QALY gained and one decreases the ICER. The EAG's deterministic ICER was £264,785; the probabilistic analyses produced a lower ICER at £225,430 which is believed to be associated with the uncertainty in the lognormal distributions and the EAG's cap ensuring that the hazard in the IsaPd arm was never higher than in the Pd arm. The ICERs improve if a severity modifier of 1.2 was assumed.

Table 28: EAG exploratory analysis results: IsaPd versus Pd

Option	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	Cost per QALY (£)*
Company's deterministic base case							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	182,769 (152,307)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
EAG exploratory analysis 1: Correction of the perceived modelling error							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	190,183 (158,486)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
EAG exploratory analysis 2: Use of independently fitted lognormal distributions for OS but constraining so that the risk in the IsaPd arm was never greater than in the Pd arm							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	248,450 (207,042)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
EAG exploratory analysis 3: Use of independently-fitted lognormal distributions for PFS							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	186,221 (155,184)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
EAG exploratory analysis 4: Costs of subsequent treatments set to that observed in ICARIA-MM							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	203,070 (169,225)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
EAG exploratory analysis 5: Using the distribution of weight rather than the mean weight							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	181,577 (151,314)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic EAG base case (EAG analyses 1, 2, 3, 4 and 5 combined)							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	264,785 (220,654)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
Probabilistic EAG base case (EAG analyses 1, 2, 3, 4 and 5 combined)							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	225,430 (187,859)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-

IsaPd – isatuximab, pomalidomide and dexamethasone; LYG - life year gained; Pd - pomalidomide and dexamethasone; QALY - quality-adjusted life year
** Numbers in parentheses are ICERs assuming a disease severity model of 1.2*

Table 29 details the results of the EAG's additional sensitivity analyses. The sensitivity analyses applied to the EAG-preferred base case resulted in a deterministic ICER range for IsaPd compared with Pd of £193,389 to £307,844 per QALY gained when assuming a severity modifier of 1.0. The lower value of the range reflects a scenario in which the company's preferred distributions to model OS are used, whilst the upper value of the range assumes that HRQoL is independent of treatment.

Table 29: EAG additional sensitivity analyses: IsaPd versus Pd (all deterministic)

Option	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	Cost per QALY (£)*
EAG's base case							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	264,785 (220,654)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
EAG sensitivity analysis 1a: Use of jointly-fitted lognormal distributions for OS							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	193,389 (161,158)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
EAG sensitivity analysis 1b: Use of exponential distributions for OS							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	249,891 (208,243)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
EAG sensitivity analysis 2: Use of a jointly-fitted RCS Weibull model for PFS							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	258,081 (215,067)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
EAG sensitivity analysis 3: Assuming that utility in a health state was independent of treatment							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	307,844 (256,537)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-

IsaPd – isatuximab, pomalidomide and dexamethasone; LYG - life year gained; Pd - pomalidomide and dexamethasone; QALY - quality-adjusted life year
** Numbers in parentheses are ICERs assuming a disease severity model of 1.2*

4.4.3.1.2 EAG exploratory analyses using SACT data (company's base case AFC)

EAG base case analysis results Table 30 presents the results of the EAG's preferred analysis. The EAG's deterministic ICER was £159,127; the probabilistic analyses produced a lower ICER at £155,596 using a disease severity modifier of 1.0. The ICERs improve to £132,606 and £129,663 if a severity modifier of 1.2 was assumed.

Table 30: EAG exploratory analysis results: IsaPd versus Pd base case AFC

Option	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	Cost per QALY (£)*
Company's deterministic base case AFC							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	124,744 (103,953)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
EAG exploratory analysis 6: Correction of the perceived modelling error							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	130,379 (108,649)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
EAG exploratory analysis 7: Use of an RCS Weibull with 3 knots for IsaPd and an RCS Weibull with 1 knot for Pd							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	153,182 (127,652)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
EAG exploratory analysis 8: Using the distribution of weight rather than the mean weight							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	124,034 (103,362)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic EAG base case (EAG analyses 6, 7, and 8 combined)							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	159,127 (132,606)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
Probabilistic EAG base case (EAG analyses 6, 7, and 8 combined)							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	155,596 (129,663)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-

AFC – after fact check; IsaPd – isatuximab, pomalidomide and dexamethasone; LYG - life year gained; Pd - pomalidomide and dexamethasone; QALY - quality-adjusted life year
** Numbers in parentheses are ICERs assuming a disease severity model of 1.2*

Table 31 details the results of the EAG's additional sensitivity analyses. The sensitivity analyses applied to the EAG-preferred base case resulted in a deterministic ICER range for IsaPd compared with Pd of £126,612 to £165,514 per QALY gained when assuming a severity modifier of 1.0 and £105,510 to £137,928 per QALY gained when assuming a severity modifier of 1.2. The lower value of the range reflects a scenario in which the company's preferred distribution to model OS for IsaPd is used, whilst the upper value of the range assumes that HRQoL is independent of treatment.

Table 31: EAG additional sensitivity analyses: IsaPd versus Pd base case AFC (all deterministic)

Option	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	Cost per QALY (£)*
EAG's base case AFC							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	159,127 (132,606)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
EAG sensitivity analysis 4a: Use of a lognormal distribution for OS for IsaPd							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	126,612 (105,510)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
EAG sensitivity analysis 4b: Use of a lognormal distribution for OS for Pd							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	165,091 (137,576)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
EAG sensitivity analysis 5: Assuming that utility in a health state was independent of treatment							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	165,514 (137,928)
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-

AFC – after fact check; IsaPd – isatuximab, pomalidomide and dexamethasone; LYG - life year gained; Pd - pomalidomide and dexamethasone; QALY - quality-adjusted life year
** Numbers in parentheses are ICERs assuming a disease severity model of 1.2*

4.4.3.2 *IsaPd versus daratumumab monotherapy*

EAG base case analysis results

Table 32 presents the results of the EAG's preferred analysis. As shown in the table, changing to the OS distributions preferred by the EAG increases the ICER from £117,709 to £298,454, the EAG base case ICER was £323,799, all ICERs using a disease severity modifier of 1.2. As the EAG asked the company late in the process to include the RCS distributions within the model, there was not time for the company to allow PSA to be run on these parameters. However, the EAG is content that the probabilistic ICER will be similar to the deterministic one as in the company's analysis the probabilistic ICER was 2% greater than the deterministic ICER.

Table 32: EAG exploratory analysis results: IsaPd versus daratumumab monotherapy

Option	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	Cost per QALY (£)*
Company's deterministic base case							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	141,251 (117,709)
Dm	[redacted]	[redacted]	[redacted]	-	-	-	
EAG exploratory analysis 9: Correction of the perceived modelling error							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	149,397 (124,497)
Dm	[redacted]	[redacted]	[redacted]	-	-	-	
EAG exploratory analysis 10: Alternative distributions for OS (RCS Weibull with 3 knots for IsaPd and an RCS lognormal with 2 knots for daratumumab monotherapy)							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	358,144 (298,454)
Dm	[redacted]	[redacted]	[redacted]	-	-	-	
EAG exploratory analysis 11: Setting the administration costs of subcutaneous injections to zero after the first dose							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	145,884 (121,570)
Dm	[redacted]	[redacted]	[redacted]	-	-	-	
EAG exploratory analysis 12: Using the distribution of weight rather than the mean weight							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	140,217 (116,848)
Dm	[redacted]	[redacted]	[redacted]	-	-	-	
Deterministic EAG base case (EAG analyses 9, 10, 11 and 12 combined)							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	388,559 (323,799)
Dm	[redacted]	[redacted]	[redacted]	-	-	-	

AFC – after fact check; IsaPd – isatuximab, pomalidomide and dexamethasone; LYG - life year gained; Pd - pomalidomide and dexamethasone; QALY - quality-adjusted life year

** Numbers in parentheses are ICERs assuming a disease severity model of 1.2*

Table 33 details the results of the EAG's additional sensitivity analyses. The sensitivity analyses applied to the EAG-preferred base case resulted in an ICER range for IsaPd compared with daratumumab monotherapy of £167,100 to £373,451 per QALY gained assuming a disease severity modifier of 1.2. The lower value of the range reflects a scenario in which a lognormal distribution for OS for IsaPd is assumed, whilst the upper value of the range assumes that utility in a health state is independent of treatment arm.

Table 33: EAG additional sensitivity analyses: IsaPd versus daratumumab monotherapy (all deterministic)

Option	LYGs	QALYs	Costs (£)	Inc. LYGs	Inc. QALYs	Inc. costs (£)	Cost per QALY (£)*
EAG's base case							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	388,559 (323,799)
Dm	[redacted]	[redacted]	[redacted]	-	-	-	
EAG sensitivity analysis 6a: Assuming a lognormal distribution for OS for IsaPd							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	200,521 (167,100)
Dm	[redacted]	[redacted]	[redacted]	-	-	-	
EAG sensitivity analysis 6b: Assuming a Weibull distribution for OS for daratumumab monotherapy							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	240,414 (200,345)
Dm	[redacted]	[redacted]	[redacted]	-	-	-	
EAG sensitivity analysis 7: Assuming that utility in a health state was independent of treatment							
IsaPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	448,141 (373,451)
Dm	[redacted]	[redacted]	[redacted]	-	-	-	

AFC – after fact check; IsaPd – isatuximab, pomalidomide and dexamethasone; LYG - life year gained; Pd - pomalidomide and dexamethasone; QALY - quality-adjusted life year
** Numbers in parentheses are ICERs assuming a disease severity model of 1.2*

4.5 Discussion

The model submitted by the company was perceived to have few errors, however, following the FACT check process an additional error was identified that was corrected by the EAG. The company and the EAG differed in terms of parameter to use within the model meaning that the ICER in the EAG's base case was considerably higher than in the company's base case. For the comparison with Pd in the original submission, the company's deterministic ICER was £182,769 whereas the EAG's deterministic ICER was £264,785. These ICERs would decrease if a disease severity modifier of 1.2 were assumed to be applicable. The company's base case AFC ICER was £103,953 with the EAG's base case ICER being £132,606; both ICERs assumed a disease severity modifier of 1.2.

For the comparison with daratumumab monotherapy, the company's deterministic ICER was £117,709 whereas the EAG's deterministic ICER was £323,799 with both estimates using a disease severity modifier of 1.2.

All ICERs would increase if the increased utility in the PFS health state ascribed to IsaPd in both the company's and the EAG's base case was to be removed; for illustrative purposes this increased the EAG's deterministic ICER by over £60,000 when IsaPd is compared with Pd, by over £5000 in the base

case AFC, and by nearly £60,000 when IsaPd is compared with daratumumab monotherapy assuming disease severity modifiers of 1.

Finally, the EAG comments that these results do not include the PAS discounts for any drug apart from isatuximab and thus the ICERs presented here may be misleading. The cost per QALY gained for IsaPd compared with Pd and for IsaPd compared with daratumumab monotherapy when other PAS discounts are incorporated into the analysis are provided in a confidential appendix to this EAG report. The sources used for the costs in the confidential appendix are shown in Table 34.

Table 34: The source for the prices used in the confidential appendix where the price differs from that used in the company's model

Treatment	Source for price used in the confidential appendix
Bendamustine	Emit
Bortezomib	Emit
Carfilzomib	PAS
Cisplatin	Emit
Cyclophosphamide (injection)	Emit
Cyclophosphamide (oral)	Emit
Daratumumab	PAS
Dexamethasone (intravenous)	Emit
Dexamethasone (oral)	Emit
Doxoribicin	Emit
Etoposide	Emit
Ixazomib	PAS
Lenalidomide	CMU
Melphalan	Emit
Panobinostat	PAS
Pomalidomide	PAS
Thalidomide	Emit

CMU – Commercial Medicines Unit; Emit – Electronic market information tool; PAS – Patient Access Scheme

5 SEVERITY MODIFIERS

In Section 3.6 of the CS, the company discusses NICE's severity modifier criteria having noted that IsaPd had been adjudged to have met the previous end of life criteria which increased the cost per QALY threshold used in the initial appraisal. In order to receive a severity modifier, the QALY shortfall for patients without the use of the intervention must be 0.85 or greater compared with an age- and sex-matched population[36] or the absolute shortfall must be 12 or more QALYs. Above either of these values, a severity modifier of 1.2 or of 1.7 is used depending on the levels of proportional shortfall or absolute shortfall. To obtain a severity modifier value of 1.7, the proportional shortfall must be at least 0.95 or the absolute QALY shortfall must be at least 18; if neither criterion is met, a severity modifier value of 1.2 is used.[54]

The company estimates that patients of the same age and sex profile as those in the decision problem (aged 65.1 year with 51.8% male) would have on average 10.75 QALYs remaining. For patients receiving daratumumab monotherapy, the company estimates that [redacted] QALYs would be accrued resulting in an absolute QALY shortfall of [redacted] and proportional QALY shortfall of [redacted]; the proportional QALY shortfall value would entitle a severity modifier of 1.2 to be used. The company's base case estimated that patients in the Pd arm would accrue [redacted] QALYs compared with 10.75 QALYs for resulting in an absolute QALY shortfall of [redacted] and proportional QALY shortfall of [redacted]. Neither value in the Pd comparison is associated with an increased severity modifier; however, the company makes the claim that Pd should have worse efficacy than daratumumab monotherapy and that the 1.2 severity modifier for daratumumab monotherapy should be applied to Pd.

In the company's base case AFC, a case for a severity modifier of 1.2 for the comparison with Pd was put forward as the company estimate that the new population (aged 71 years) would have on average 8.67 QALYs remaining. For patients receiving Pd, the company estimates that [redacted] QALYs would be accrued resulting in an absolute QALY shortfall of [redacted] and proportional QALY shortfall of [redacted]; the proportional QALY shortfall value would entitle a severity modifier of 1.2 to be used. In the EAG base case AFC Pd treatment was associated with [redacted] QALYs would be accrued resulting in an absolute QALY shortfall of [redacted] and proportional QALY shortfall of [redacted] (as the EAG estimated 8.78 QALYs for the general population); thus, the EAG also estimate a disease severity modifier of 1.2. However, the EAG has strong reservations as to whether the naïve comparison using SACT data is appropriate.

In the EAG base case analysis for IsaPd compared with daratumumab monotherapy the estimated QALYs gained associated with daratumumab monotherapy are [redacted] which would mean an absolute QALY shortfall of [redacted] and proportional QALY shortfall of [redacted] which would imply a severity modifier value of 1.2. In the EAG base case analysis for IsaPd compared with Pd, the QALYs gained

associated with Pd are [redacted] which would mean an absolute QALY shortfall of [redacted] and proportional QALY shortfall of [redacted], implying a severity modifier of 1.0. The EAG's values for the age- and sex-matched population are moderately different to the company's through the use of a different tool[56] which predicted 10.95 QALYs remaining, which is more favourable to the intervention.

The EAG highlights that in the company's initial base case analyses the historic end of life criteria would be unlikely to be triggered in the comparison with Pd as the expected length of life for patients on Pd ([redacted] years) is considerably greater than 24 months. The expected length of life for patients on daratumumab monotherapy is marginally greater than 24 months at [redacted] years.

6 OVERALL CONCLUSIONS

The main source of evidence in the CS for the comparison of IsaPd with Pd was one open-label RCT (ICARIA-MM). In the 4L population, the median PFS was greater in the IsaPd arm (12.39 months [95% CI: 7.425, 27.663]) than in the Pd arm (6.54 [95% CI: 4.468, 10.086]), and the stratified HR was 0.536 (95%: CI 0.343, 0.840), which represents a 46.4% risk reduction of disease progression or death in favour of IsaPd. 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. After fact check, the company provided a revised base case where SACT data for IsaPd and Pd were naïvely compared.

For a comparison with daratumumab monotherapy the company conducted a naïve indirect comparison using SACT data. As acknowledged by the company such comparisons are prone to bias so the results should be treated with caution (these comments are equally applicable to the company's new base case AFC).

The company submitted an economic model which indicated that the deterministic cost per QALY gained of IsaPd compared with Pd was £152,307 and was £117,709 when compared with daratumumab monotherapy, when disease severity modifiers of 1.2 were used. The base case AFC reduced the ICER of IsaPd compared with Pd to 103,953 using a disease severity modifier of 1.2.

For the comparison with Pd, the EAG preferred alternative distributions to fit OS and PFS, included the costs associated with subsequent treatments used in ICARIA-MM and used a distribution of weight rather than a single point. These amendments resulted in a deterministic ICER of £264,785 (£220,654 probabilistic) assuming a disease severity modifier of 1.0. A sensitivity analyses that assumed that utility in the PFS state was independent of treatment increased the ICER to £307,884.

For the comparison with Pd using the company's base case AFC, the EAG preferred alternative distributions to fit OS and used a distribution of weight rather than a single point. This increased the deterministic ICER to £132,606 and the probabilistic ICER to £129,663. However, the EAG has strong reservations as to whether the naïve comparison using SACT data is appropriate.

For the comparison with daratumumab monotherapy, the EAG preferred alternative distributions to fit OS and removing the administrative costs associated with subcutaneous injections after the first dose. These amendments resulted in a deterministic ICER of £323,799 assuming a disease severity modifier

of 1.2. A sensitivity analyses that assumed that utility in the PFS state was independent of treatment increased the ICER to £373,451.

The EAG highlights that these values do not include PAS discounts related to interventions other than isatuximab; results including these PAS discounts are contained in a confidential appendix to this report.

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8. APPENDICES

Appendix 1: Technical appendix – instructions for implementing the EAG's exploratory analyses within the company's model

Scenario		Instructions
For the Pd comparison		
EAG exploratory analysis	1	Set K11 to 1 in the 'Settings' worksheet
	2	Select independently-fitted lognormal distributions for OS using the company's drop-down boxes. Note a new sheet 'Cap HR' has been added by the EAG and formula changed in the 'Comp1 Calc' worksheet in column DF. A switch named 'Override' has been added in the 'SelectDist_OS' worksheet which is activated when both IsaPd and Pd are independently-fitted lognormals.
	3	Select independently-fitted lognormal distributions for PFS using the company's drop-down boxes.
	4	Load the company's saved scenario that includes the costs of subsequent treatment from ICARIA-MM. This is named '4L UK (Pd Comparison, ICARIA subseq. tx)'
	5	Change cells G10 and G43 to the value in L10 in the 'Costs_MedAdmin' worksheet
EAG sensitivity analysis	1a	Select jointly fitted lognormal distributions for OS from the company's drop-down boxes
	1b	Select exponential distributions for OS from the company's drop-down boxes
	2	Select jointly-fitted RCS Weibull distributions for PFS from the company's drop-down boxes
	3	Copy cells R9:V10 in the 'Utilities_State' worksheet into cells D9:H10
For the Pd comparison (base case AFC)		
EAG exploratory analysis	6	Set K11 to 1 in the 'Settings' worksheet
	7	Select the distribution for OS for IsaPd to be an RCS Weibull with 3 knots using the company's drop-down box. Select the distribution for OS for Pd to be an RCS Weibull using the company's drop-down box
	8	Change cells G10 and G43 to the value in L10 in the 'Costs_MedAdmin' worksheet
EAG sensitivity analysis	4a	Select a lognormal distribution for OS for IsaPd from the company's drop-down boxes
	4b	Select a lognormal distribution for OS for Pd from the company's drop-down boxes
	5	Copy cells R9:V10 in the 'Utilities_State' worksheet into cells D9:H10
For the daratumumab monotherapy comparison		
EAG exploratory analysis	9	Set K11 to 1 in the 'Settings' worksheet
	10	Select the distribution for OS for IsaPd to be an RCS Weibull with 3 knots using the company's drop-down box. Select the distribution for OS for daratumumab monotherapy to be an RCS lognormal with 2 knots using the company's drop-down box
	11	Set cell E57 in the 'Costs_MedAdmin' worksheet to zero
	12	Change cells G10 and G43 to the value in L10 in the 'Costs_MedAdmin' worksheet
EAG sensitivity analysis	6a	Select a lognormal distribution for OS for IsaPd from the company's drop-down boxes
	6b	Select a Weibull distribution for OS for daratumumab monotherapy from the company's drop-down boxes
	7	Copy cells R9:V10 in the 'Utilities_State' worksheet into cells D9:H10

Single Technology Appraisal

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [Review of TA658]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

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If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 30 November 2023** 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.

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Issue 1 Potential issue with interpretation of clinician advice on daratumumab monotherapy

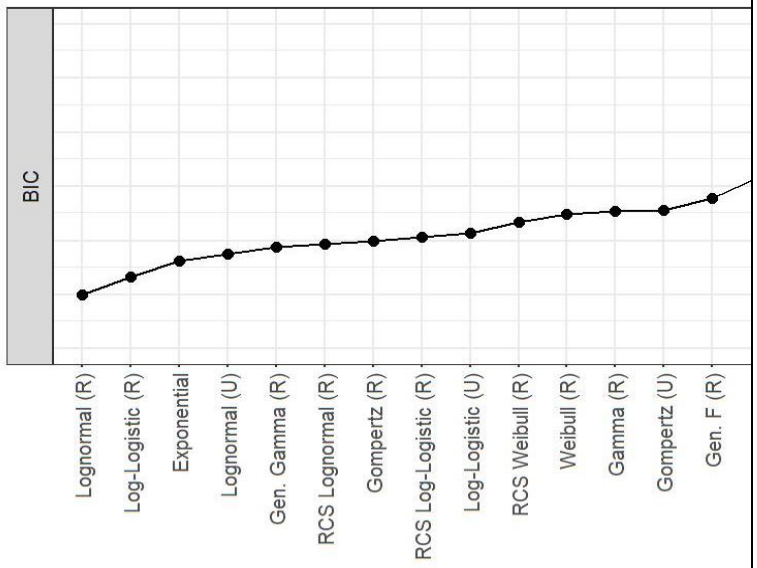
Description of problem	Description of proposed amendment	Justification for amendment
The EAG report Page 38, Paragraph 3 states the following: "*Clinical advice to the EAG suggests that because data collection in SACT was earlier for daratumumab monotherapy than for IsaPd, this potentially means that the patients being treated with daratumumab monotherapy in SACT are less pre-treated and would be easier to achieve disease control; the results could therefore* ***be unfavourable to daratumumab monotherapy***. " The company suspect that the clinical advice to the EAG may be misinterpreted. Although DARA SACT data collection started earlier than IsaPd SACT, the patients receiving both treatments are likely to be equally pre-treated as both IsaPd and daratumumab monotherapy are prescribed as 4th line therapies. If the clinical advice to the EAG is correctly reported, then the logical interpretation that follows would be that the current comparison is	We propose that the wording is amended to the following to ensure clarity in interpretation. "Clinical advice to the EAG suggests that because data collection in SACT was earlier for daratumumab monotherapy than for IsaPd, this potentially means that the patients being treated with daratumumab monotherapy in SACT are less pre-treated and would be easier to achieve disease control; the results could therefore be more unfavourable *for daratumumab monotherapy had patients similar to those receiving IsaPd had received treatment with daratumumab in SACT."*	Correcting this issue would ensure appropriate interpretation of the likely outcomes with IsaPd if patients treated with IsaPd were more similar to those that received daratumumab monotherapy in practice.

Description of problem	Description of proposed amendment	Justification for amendment
unfavourable to IsaPd and potentially underestimates the treatment benefit for IsaPd vs Daratumumab monotherapy. Had a cohort of less pre-treated patients been treated with IsaPd, the treatment outcomes may be improved with IsaPd than that observed in SACT.		

Issue 2 Minor issues related to incorrect pages and sources referenced

Description of problem	Description of proposed amendment	Justification for amendment
The EAG report Page 49, Table 10, Row 7 states “Mortality – general population constraint*” was “derived from interim life tables for England **2016-2018**”. General population mortality values in the analysis were derived from the life tables for England **2018-2020.**	We propose this is amended to the following “Derived from interim life tables for England **2018-2020**”.	Correction of this issue will ensure accurate reflection of the company submission.
The EAG report Page 24, paragraph 4 states “A flow diagram of patient flow through the ICARIA-MM study is presented in **Figure 12, page 39** of the CS”	We propose this is amended to the following “A flow diagram of patient flow through the ICARIA-MM study is presented in **Figure 3, page 48**”	Correction of this issue will ensure accurate reflection of the company submission.

Description of problem	Description of proposed amendment	Justification for amendment
The EAG report Page 25, paragraph 1 states “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**”	We propose this is amended to the following “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 46 to 49**”	Correction of this issue will ensure accurate reflection of the company submission.
The EAG report Page 26, paragraph 1 states “Permitted and disallowed concomitant treatments are detailed in the CS, Table 6, page 33. The company’s clarification response to question A4[17]”	We propose this is amended to the following “Permitted and disallowed concomitant treatments are detailed in the CS, Table 6, page 33. The company’s clarification response to question A4[15]”	Correction of this issue will ensure accurate reflection of the company submission and accurate referencing.
The EAG report Page 26, paragraph 3 states “The company’s clarification response to question A4[17]”	We propose this is amended to the following “The company’s clarification response to question A4[15]”	Correction of this issue will ensure accurate reflection of the company submission and accurate referencing.
The EAG report Page 28 paragraph 1 states “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.[17] ”	We propose this is amended to the following “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 **and in the reference pack for ID4067 Review submission**.[15]”	Correction of this issue will ensure accurate reflection of the company submission and accurate referencing.

Description of problem	Description of proposed amendment	Justification for amendment
The EAG report Page 52, Figure 7 is an incorrect figure of BIC rankings for IsaPd and Pd OS.	The correct ranking of IsaPd and Pd joint OS curves by BIC and that reported in Figure 16 of Appendix R is presented in Figure 1 below. **Figure 1: Fit statistics for parametric distributions fit to OS for the 4th line population of ICARIA-MM**  Abbreviations: BIC, Bayesian Information Criterion; OS, overall survival; R, restricted; RCS, restricted cubic spline; U, unrestricted.	Correction of this issue will ensure accurate reflection of the company submission.

Single Technology Appraisal

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [Review of TA658]

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Issue 1 Incorrect interpretation of evidence presented in company submission documents

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
On page 49 of the 'ID4067 MM-Isatuximab Report sent to NICE after Fact Check 18th Dec' EAG states the following "The EAG notes that IsaPd SACT KM OS presented in additional evidence Figure 4 (reproduced in Figure 6) is different to the IsaPd SACT KM OS presented in CS Figure 7 (reproduced in Figure 7)".	The IsaPd SACT KM OS presented in Figure 4 (and reproduced in Figure 6) uses the same underlying data as presented in CS Figure 7. The visual difference is attributable to the change in the scale of the y-axis from months (in Figure 4) to years (in Figure 7). We propose that this sentence is removed to avoid confusion.	The statement as presented is misleading. The data informing both figures use the same data and therefore there is no discrepancy.	The company's statement that the underlying data are the same does not appear to be supported by Figures 6 and 7. "The EAG notes that the IsaPd SACT KM OS presented in additional evidence Figure 4 (reproduced in **Error! Reference source not found.**) does not appear to be the same as the IsaPd SACT KM OS presented in CS Figure 7 (reproduced in **Error! Reference source not found.**) with differences including the shape of the tail and follow-up length. The EAG also notes that Figure 6 was plotted by the company using reconstructed IPD whereas Figure 7 was extracted directly from SACT data using SACT IPD.[24]"

Issue 2 Need for greater clarity in evidence used to inform statement

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
On page 123, the following is stated, 'The EAG highlights that in the company's base case analyses the historic end of life criteria would be unlikely to be triggered in the comparison with Pd as the expected length of life for patients on Pd ([redacted] years) is considerably greater than 24 months. The expected length of life for patients on daratumumab monotherapy is marginally greater than 24 months at [redacted] years.' We propose that the wording should be modified to clarify that the statement regarding end of life being unlikely to be triggered is specifically in reference to when Pd data is derived from the ICARIA-MM trial, which informed the company's initial base case (before AFC).	We propose the following amendment in italics: The EAG highlights that in the company's *initial base case analyses* the historic end of life criteria would be unlikely to be triggered in the comparison with Pd as the expected length of life for patients on Pd ([redacted] years) is considerably greater than 24 months. The expected length of life for patients on daratumumab monotherapy is marginally greater than 24 months at [redacted] years.	Provides greater clarity on which evidence is referenced within this statement.	Amended as suggested