Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma. A Single Technology Appraisal.

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None of the authors has any conflicts of interest to declare. Conflicts related to our clinical advisors are presented in the acknowledgements.

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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. John Stevens and Martin Orr critiqued the statistical aspects of the submission. Matt Stevenson and Aline Navega Biz critiqued the health economic analysis submitted by the company. All authors were involved in drafting and commenting on the final report.

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Abbreviations

3L	Third-line
4L	Fourth-line
5L	Fifth-line
AE	Adverse event
BIC	Bayesian Information Criterion
BNF	British National Formulary
BOR	Best overall response
BSA	Body surface area
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CDF	Cancer Drugs Fund
CS	Company's submission
CSR	Clinical Study Report
DCO	Data cut-off
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DVd	Daratumumab, bortezomib and low-dose dexamethasone
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire with 30 items
EORTC-QLQ-MY20	European Organisation for Research and Treatment of Cancer Quality of Life Multiple Myeloma Specific Module with 20 items
EOT	End of treatment
EQ-5D-5L	EuroQoL Group self-report questionnaire with 5 dimensions (3 level)
EQ-5D-5L	EuroQoL Group self-report questionnaire with 5 dimensions (5 level)
ERG	Evidence Review Group
GEE	Generalised estimating equation
GHS	Global health status
HR	Hazard ratio
HRQoL	Health-related quality of life
ICARIA-MM	Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma

ICER	Incremental cost-effectiveness ratio
IMWG	International Myeloma Working Group
IRC	Independent Response Committee
IRT	Interactive response technology
IsaPd	Isatuximab, pomalidomide and low-dose dexamethasone
ISS	International Staging System
KM	Kaplan-Meier
LYG	Life year gained
MAIC	Matching-adjusted indirect comparison
MM	Multiple myeloma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
ORR	Overall response rate
OS	Overall survival
PanVd	Panobinostat, bortezomib, dexamethasone
PAS	Patient Access Scheme
Pd	Pomalidomide and low-dose dexamethasone
PFS	Progression-free survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Services
QALY	Quality-adjusted life year
RCS	Restricted cubic spline
RCT	Randomised controlled trial
RDI	Relative dose intensity
RRMM	Relapsed and/or refractory multiple myeloma
SAE	Serious adverse event
SD	Standard deviation
STA	Single Technology Appraisal
TEAE	Treatment-emergent adverse event
TTD	Time to treatment discontinuation
TTP	Time to progression

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company provided an appropriate description of multiple myeloma (MM), with a focus on relapsed and refractory MM (RRMM), the current practice guidelines regarding lines of treatment and the potential positioning of isatuximab, pomalidomide and low-dose dexamethasone (IsaPd) in the treatment pathway. The proposed positioning of IsaPd in the company base case was narrower than the anticipated market authorisation, with the company assuming that IsaPd would be used in patients who have received after three prior lines of treatment, including lenalidomide, and would be used in fourth-line (4L) rather than in third-line. The main comparator was assumed to be pomalidomide and low-dose dexamethasone (Pd) although to fulfil the NICE scope a comparison was made against panobinostat, bortezomib and dexamethasone (PanVd). The company stated that it did not believe that PanVd was an appropriate comparator due to the toxicity associated with this intervention.

Expert clinical opinion provided to the ERG was divided on whether PanVd was an appropriate comparator for IsaPd. One clinician stated that PanVd was rarely used due to toxicity and the perceived lack of response compared with alternative therapies, however, other clinicians stated that PanVd was used in several units and that toxicity concerns would be managed with changes to the dose or schedule. Whilst these experts stated that PanVd was generally used at fifth-line (5L) this was because daratumumab monotherapy is only permitted to be used, via the Cancer Drugs Fund (CDF) as a 4L treatment. However, were daratumumab monotherapy not available, as NICE do not consider drugs within the CDF to be comparators, these clinicians stated that PanVd would be used at 4L.

1.2 Summary of the clinical effectiveness evidence submitted by the company

The clinical evidence relating to IsaPd for treating RRMM is based on the ICARIA-MM trial, a Phase III open-label randomised controlled trial (RCT) of patients with at least two prior lines of treatment. The ERG is confident that no additional studies (published or unpublished) of IsaPd for treating RRMM are likely to have been missed.

The ERG is confident that the relevant population, intervention and comparator have been included in the company's submission (CS). The primary outcome of the ICARIA-MM trial was progression-free survival (PFS), assessed from the date of randomisation to the date of first documentation of progressive disease or the date of death from any cause, whichever came first, at the cut-off date (11th October 2018), which is an acceptable primary outcome according to the European Medicines Agency (EMA), provided that overall survival (OS) demonstrates a trend towards superiority. In the 4L population, the median PFS was greater in the IsaPd arm (13.31 months [95% CI: 7.425, not calculable]) than in the Pd arm (7.82 [95% CI: 4.468, 11.072]), and the stratified (by age) hazard ratio (HR) was 0.598 (95%: CI

0.348, 1.030, *p*=0.0611), which the CS states represents a 40.2% risk reduction of disease progression or death in favour of IsaPd compared with Pd. The EMA suggests that OS should demonstrate a trend towards superiority if PFS is used as a primary outcome. Mortality events were reported in 21.2% and 39.7% of 4L patients in the IsaPd and Pd arms, respectively, with a median OS of 14.36 months (95%: CI 11.565, not calculable) in the Pd arm whilst the median OS had not been reached in the IsaPd arm (stratified HR 0.494 [95% CI 0.240, 1.015], *p*=0.0502), which indicates a trend for greater median OS in the IsaPd arm. However, the OS data were immature and final OS analyses are planned once 220 deaths have been observed (anticipated in Q2 2021). In the 4L population, there were 34 death events; 11 (21.2%) in the IsaPd arm and 23 (39.7%) in the Pd arm at data cut-off. The effect of IsaPd on OS may have been impacted by an imbalance between the trial arms in the proportion of patients who received subsequent daratumumab. Overall response rates and median time to progression were higher in the IsaPd arm of the 4L population than the Pd arm. The median duration of response was not calculable for both the IsaPd and Pd arms in the 4L population, and no clinically meaningful difference between treatment arms on European Organisation for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire with 30 items (EORTC-QLQ-C30) scores and subscale scores, suggesting no quality of life detriment of IsaPd in relation to treatment with Pd. In terms of adverse events, IsaPd appears to be generally well tolerated.

IsaPd and PanVd were not part of a connected network of evidence and were compared using a matching-adjusted indirect comparison (MAIC) of IsaPd from the ICARIA-MM study and PanVd from the PANORAMA-2 study (patients with RRMM who had received at least two prior treatments, including an immunomodulatory drug, and who had progressed on or within 60 days of their last Bortezomib-based therapy). The company included various potential or known prognostic factors and/or treatment effect modifiers as covariates in its MAIC model in order to re-weight the PFS data from the ICARIA-MM IsaPd arm to match the distribution of patient characteristics of the PanVd arm of the PANORAMA-2 study. The results appeared favourable to IsaPd with a HR of 0.369 (95% CI 0.259 to 0.526) for PFS, and a HR of 0.642 (95% CI: 0.38, 1.082) for OS.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The first key uncertainty relates to the open-label nature of the trial, which may have introduced measurement bias, and may have altered patterns of oral medication use by patients (e.g. oral pomalidomide, the relative dose intensity of which was higher in the Pd arm than in the IsaPd arm). The impact of this element of study design is difficult to assess; and its impact on the results of the study is unclear.

The second key uncertainty relates to the post-hoc analysis and reporting of patients in the ICARIA-MM study at 4L of treatment. The 4L population is directly relevant to the proposed positioning of

IsaPd within the treatment pathway, however the ERG has some reservations with this *post hoc* approach, as it was not a stratified group and does not have the protection of the randomisation when making comparisons between treatments.

A discrepancy between the arms in the use of subsequent daratumumab introduces uncertainty in the measurement of OS. Since subsequent daratumumab use (at 5L) is inconsistent with the current UK clinical management pathway for RRMM, this may compromise the generalisability of the ICARIA-MM study results to the UK context.

Within the MAIC it is not clear whether the covariates represent all relevant prognostic factors and/or treatment effect modifiers and the final comparison may be biased. Various survival models were fitted to the progression-free survival and OS data; however, the ERG has concerns with the modelling, including the way the treatment effect(s) were defined in the models, mixing baseline estimates from parametric models and estimates of treatment effects from Cox regression, and the use of hazards ratios from Cox regression models in survival models that are not proportional hazards models, and is not confident with making inferences from them.

1.4 Summary of the cost effectiveness evidence submitted by the company

Following the clarification process, the ERG believes the company's model to be generally well programmed and free from major errors. In its initial submission, the company's model was more complex and required several assumptions in order to explicitly distinguish between average time spent on and off 4L treatment. Whilst the model structure remained unaltered following the clarification process, the parameters were changed such that the model essentially was a standard partitioned survival model oncology approach using three-states (progression-free, progressed, and dead) with time on treatment modelled independently. Pivotal data for the comparison of IsaPd and Pd were taken from the ICARIA-MM study. For the comparison of IsaPd and PanVd, the company had to rely on a MAIC, which the company stated was exploratory and subject to limitations.

Within its base case analysis, the company maintained the use of estimated Patient Access Scheme prices (PASs) for pomalidomide, daratumumab and panobinostat; this is contrary to NICE guidance. The company did present results for its base case with the PAS discounts removed, which for ease of reading the ERG has termed the company's base case. The probabilistic results from this analysis indicated that IsaPd would generate an additional 1.055 quality-adjusted life years (QALYs) compared with Pd and an additional 0.791 QALYs compared with PanVd. These values result in an incremental cost-effectiveness ratio (ICERs) for IsaPd versus Pd of £130,321 per QALY gained and an ICER for IsaPd versus PanVd of £248,197 per QALY gained.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG identified seven limitations within the company's model and reporting of results. These were: i) identification of perceived modelling errors; ii) the time horizon is too short to capture all of the gains associated with IsaPd treatment; iii) the lack of comprehensive reporting of sensitivity analyses relating to the functions used for time-to-event data; iv) potentially inaccurate estimation of drug acquisition and administration costs; v) that drugs assumed to be used in 5L would not be used in the NHS in England; vi) potential face validity violations in the utilities sampled within the probabilistic sensitivity analyses; vii) and underestimation of uncertainty. The ERG explored the impact of amending some of these limitations; these did not markedly affect the ICER.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The clinical evidence for IsaPd for treating RRMM is based on a Phase III RCT (ICARIA-MM), which used a centralised computer-based method of allocation, and all outcomes reported on were pre-specified.

The mathematical model submitted following the clarification was largely appropriate for the decision problem. The company responded to the clarification questions raised and undertook the analyses requested.

1.6.2 Weaknesses and areas of uncertainty

The ICARIA-MM study used an open-label design, which may have impacted on measurements taken and also on patients' self-administration of pomalidomide.

Results for the population of interest, patients at 4L, were analysed and reported from the ICARIA-MM study post-hoc, which was not a stratified group and does not have the protection of the randomisation when making comparisons between treatments.

The OS results of the ICARIA-MM study may not be generalisable to England due to the differential subsequent use of daratumumab at 5L between the trial arms.

There was not a connected network of evidence to allow a more robust estimation of the relative clinical efficacy of IsaPd and PanVd.

Minor limitations were identified by the ERG in relation to the construction of the model and the presentation of the results.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG made two sets of changes to the company's base case to generate an ERG-preferred base case. Firstly, it corrected the perceived errors and secondly it extended the time horizon from fifteen to twenty years. The cumulative impact of these changes increased the probabilistic ICER for IsaPd versus with Pd to £133,461 per QALY gained and decreased the probabilistic ICER for IsaPd versus PanVd to £238,300 per QALY gained. Scenario analyses conducted by the ERG included: the use of alternative functions for OS data, time to treatment discontinuation data, and time to PFS data; assuming no drug wastage; and assuming 100% relative dose intensity for all 4L drugs. The range in the deterministic ICER when applying the sensitivity analyses to the ERG-preferred base case was £103,095 to £213,105 per QALY gained for IsaPd compared with Pd and £165,233 to £365,613 per QALY gained for IsaPd compared with PanVd. The lower value of the ranges are associated with an assumption of no drug wastage and the use of a jointly-fitted lognormal model with a treatment effect covariate for OS, whilst the upper value of the ranges is associated with the use of a jointly-fitted log-logistic model with a treatment effect covariate for TTD. If PanVd was a valid comparator then it was estimated that PanVd would dominate Pd, although the limitations of the MAIC need to be considered when evaluating this comparison.

These values presented in this report do not incorporate the commercial-in-confidence PAS discounts for interventions other than isatuximab; the results which include these discounts are contained in a confidential appendix to this report.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

Multiple myeloma (MM) is a malignant, haematopoietic tumour of plasma cells characterised by a clonal proliferation of bone marrow plasma cells.[1] Relapsed and refractory MM (RRMM) is defined as disease that becomes non-responsive whilst on treatment, or which progresses within 60 days of last therapy in patients who achieved at least a minimal response.[2] The company provide a comprehensive account of MM in terms of epidemiology, prognosis, and impact on patients' lives in Section B.1.3 of the company submission (CS).[3]

2.2 Critique of company's overview of current service provision

The CS[3] describes the clinical pathway for treating patients with MM and also indicates the proposed positioning of isatuximab, pomalidomide and low-dose dexamethasone (IsaPd) (reproduced as Figure 1). Whilst the company expects that the indication for isatuximab will be "*in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and proteasome inhibitor and have demonstrated disease progression on the last therapy*" the company anticipate that IsaPd will be used in patients who have received at least three prior lines of treatment, including lenalidomide, and would be used in fourth-line (4L). In line with recommendations from NICE those interventions within the Cancer Drugs Fund (CDF) were not considered comparators within this appraisal.

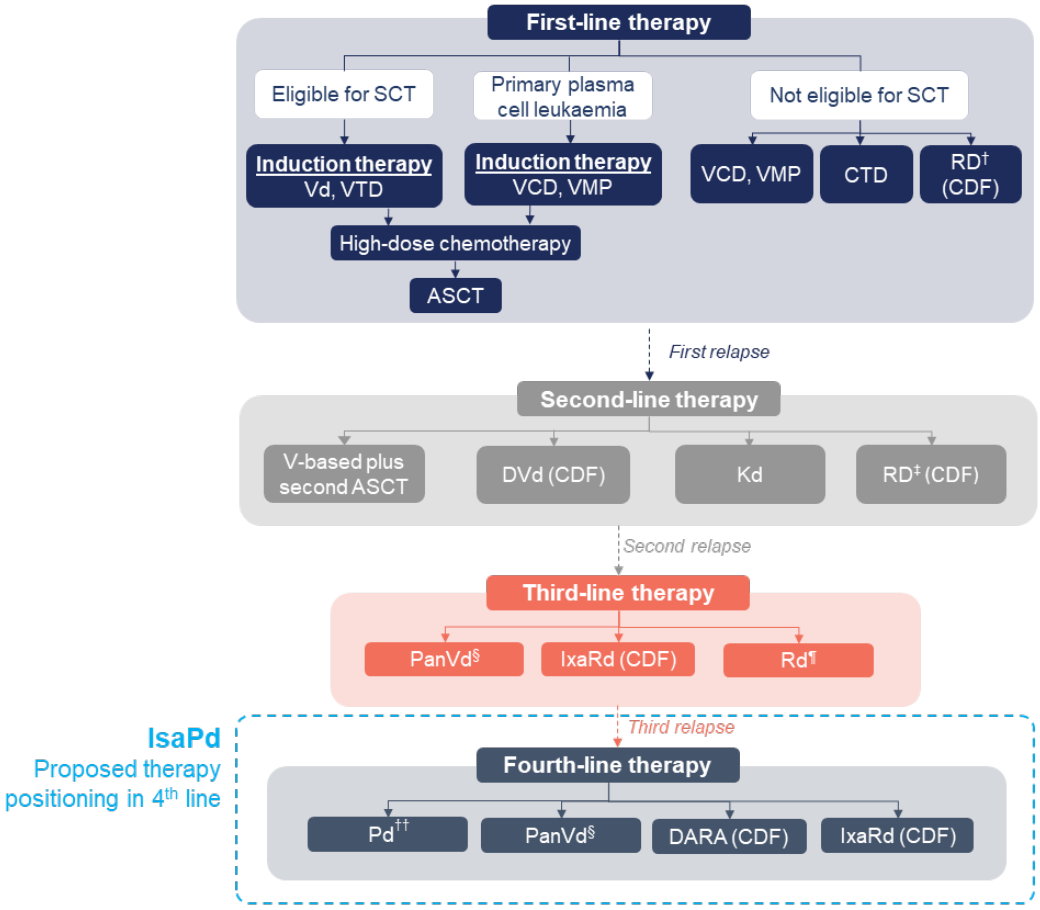
Clinical advice received by the ERG was broadly supportive of the company's description of the treatment pathway although the ERG's clinical advisors commented that: the pathway would be correct for those patients who are diagnosed now, however, patients currently at third-line (3L) or 4L may have had different preceding treatments; that treatments that are provided through the CDF (lenalidomide and dexamethasone; daratumumab, bortezomib with low-dose dexamethasone (DVd); and daratumumab monotherapy) are being widely used; and that it is possible for stem cell transplant to be used more than once. A stipulation for daratumumab monotherapy within the CDF was that it was used in 4L; as such, in the real-world setting Pd and panobinostat, bortezomib, and dexamethasone (PanVd) would be typically used at later lines. Daratumumab monotherapy is not a comparator in this appraisal as NICE does not allow drugs within the CDF to be comparators, leaving the comparators to IsaPd as Pd and PanVd.

Clinical opinion was divided on the frequency of use of PanVd in current practice although all noted the toxicity of the therapy. One clinician stated that PanVd is rarely used because of the toxicity of the

regimen and perceived lack of response when other alternatives are available, whereas other experts stated that PanVd was used in several units with dose or schedule adjustments used to manage toxicities.

Furthermore, clinical advice to the ERG anticipated that in the future the proportion of patients eligible for IsaPd is likely to decline due to the use of DVd in second-line or due to the use of daratumumab in combination with other agents at first-line, as patients who are refractory to an anti-CD38 agent were excluded from the ICARIA-MM randomised controlled trial (RCT).[4] However, clinicians stated that they would use IsaPd even in daratumumab-exposed patients provided they were not refractory to daratumumab in a prior line of therapy and had a non-anti-CD38-based treatment inbetween.

Figure 1: The company's diagram of the treatment pathway for people with MM and the proposed positioning of IsaPd



Source: adapted from NICE guideline on diagnosis and management of myeloma [NG35] [5]

Abbreviations: ASCT, autologous stem cell transplant; CDF, Cancer Drugs Fund; CTD, cyclophosphamide, thalidomide, dexamethasone; DARA, daratumumab monotherapy; DVd, daratumumab, bortezomib, low dose dexamethasone; IsaPd, isatuximab, pomalidomide, low dose dexamethasone; IxaRd, ixazomib, lenalidomide, low dose dexamethasone; kd, carfilzomib, low dose dexamethasone; PanVd, panobinostat, bortezomib, dexamethasone; PI, proteasome inhibitors; Pd, pomalidomide, low dose dexamethasone; Rd, lenalidomide, low-dose dexamethasone; RD, lenalidomide, dexamethasone; SCT, stem cell transplant; V, bortezomib; VCD, bortezomib, cyclophosphamide, dexamethasone; VD, bortezomib, low dose dexamethasone; VMP, bortezomib, melphalan, prednisone; VTD, bortezomib, thalidomide, dexamethasone;

†If lenalidomide is contra-indicated to/not tolerated by the patient and if the manufacturer provides lenalidomide according to the commercial agreement. ‡If patients have received only one previous therapy, which included bortezomib, and if the manufacturer provides lenalidomide according to the commercial agreement. §Panobinostat provided by the manufacturer at the discount agreed in the patient access scheme. ¶Drug cost of lenalidomide for patients who remain on treatment for more than 26 cycles must be met by the manufacturer. ††Pomalidomide provided by the manufacturer at the discount agreed in the patient access scheme.

2.3 Critique of company's definition of the decision problem

2.3.1 Population

The population within the company's base case is narrower than that specified within the NICE scope[6] in that the company have restricted IsaPd use to those at 4L. Supplementary analyses were provided for patients who have only received two prior lines of therapy and for those at fourth-line or later.

2.3.2 Intervention

The intervention described in the CS is consistent with the final NICE scope,[6] which is the use of isatuximab, a humanised monoclonal antibody which binds to cell surface glycoprotein CD38, in combination with pomalidomide and dexamethasone. A regulatory submission for IsaPd was submitted to the European Medicines Agency (EMA) in April 2019 with a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) expected in early 2020, and regulatory approval expected in mid-2020. The expected indication has been described in Section 2.2.

IsaPd has three components each with different posologies. Isatuximab is infused at a dose of 10mg/kg weekly for four weeks, and then every two weeks, pomalidomide is taken orally for the first 21 days of each 28-day cycle, whilst dexamethasone (40mg, reduced to 20mg in patients aged 75 years or older) which can be administered intravenously or orally, is provided on the same days, in advance of isatuximab, to reduce the risk and severity of infusion reactions.

2.3.3 Comparators

The comparators listed in the final NICE scope[6] are pomalidomide and low-dose dexamethasone (Pd) and panobinostat, bortezomib and dexamethasone (PanVd). The company's base case focusses on Pd as the comparator, as it was stated that "*feedback from clinical experts during a Sanofi Advisory Board have indicated that this combination appears to be reserved for later line (i.e. ≥5th line) mainly due to its associated toxicities. This view is supported by market share data acquired by Sanofi. Similar views have been documented in previous NICE submissions (TA427, TA510).*" This position was not universally supported by the clinicians providing advice to the ERG. One clinician agreed with the company, but two believed that PanVd was used in several units with dose and schedule changes applied to manage toxicity. These clinicians stated that PanVd was typically used at 5L although this was due to NICE guidance for daratumumab monotherapy rather than for clear clinical reasons. Daratumumab monotherapy has been recommended for use in the CDF only at 4L, meaning that if clinicians wish to try multiple treatments including daratumumab monotherapy beyond 3L, that daratumumab monotherapy would be used at 4L, with Pd and PanVd being used at later lines. As NICE do not allow interventions on the CDF to be comparators in a single technology appraisal (STA), it was assumed that PanVd, where used, would be used at 4L for this decision problem, along with Pd.

Despite the company believing PanVd was not a comparator it undertook an exploratory analysis of IsaPd compared with PanVd "*in order to meet the requirements of the scope*" using a matching-adjusted indirect comparison (MAIC) as IsaPd and PanVd were not part of a connected network of evidence.

The constituent parts of PanVd were assumed to be administered as follows: panobinostat (20mg) was assumed to be provided orally on six days across a three-week period, for a maximum of 48 weeks;

bortezomib (1.3mg/m^2) was provided via injections on four days of a three-week period for the first 24 weeks, and then on two days of a three-week period for an additional 24 weeks. Dexamethasone was provided orally, at a dose of 20mg/day, eight times across a three-week period, for a maximum of 48 weeks.

2.3.4 Outcomes

The outcomes in the CS are in line with those in the final scope issued by NICE.[6] The company has also chosen to present results estimated within a mathematical model in terms of cost per life year gained (LYG).

2.3.5 Other relevant factors

A Patient Access Scheme (PAS) for isatuximab has been agreed with the Department of Health and Social Care; this takes the form of a simple discount of [redacted] of the list price, resulting in post-PAS costs of [redacted] for a 100mg vial and [redacted] for a 500mg vial. Pomalidomide and panobinostat, which are direct comparators at 4L, also have agreed simple PAS discounts in place; however, these are commercial-in-confidence. Lenalidomide, which could be used as a fifth-line (5L) treatment in the model also has a commercial-in-confidence PAS which is a simple discount. In line with the recommendation from NICE, all cost-effectiveness results presented in this document use the list prices for all drugs, except isatuximab, with an additional confidential appendix providing the results when the PAS for other interventions are applied.

3 CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the clinical effectiveness evidence contained within the CS[3] for IsaPd for treating RRMM. Section 3.1 provides a critique of the company's systematic review of clinical and safety evidence. Section 3.2 provides a summary of the clinical effectiveness and safety results together with a critique of the included study. Sections 3.3 to 3.5 present the indirect comparisons prepared by the company and additional work undertaken by the ERG. Section 3.6 provides the conclusions of the clinical effectiveness section.

3.1 Critique of the methods of review(s)

The company undertook a systematic literature review to identify all clinical evidence regarding the efficacy and safety of IsaPd and relevant comparators for the treatment of RRMM in adult patients who have received at least two lines of treatment. The systematic review methods for the clinical evidence are detailed in Section B.2.1 of the CS and CS Appendix D.[3]

3.1.1 Searches

The company performed one clinical effectiveness search to identify all clinical and safety studies of isatuximab and its comparators (bortezomib, carfilzomib, daratumumab, dexamethasone, elotuzumab, ixazomib, lenalidomide, melphalan panobinostat, pomalidomide, thalidomide, vorinostat, and bendamustine) for the treatment of RRMM in patients who have received at least two lines of treatment.

Several electronic bibliographic databases were initially searched covering the period from inception to October 2018; these were: MEDLINE and Epub Ahead of Print, In Process and & Other Non-Indexed Citations and Daily [via Ovid], Embase [via Ovid], Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials [via Wiley]), Health Technology Assessment database and Database of Abstracts of Reviews of Effects [via CRD], and several cancer/multiple myeloma conference proceedings websites (American Society of Clinical Oncology, European Society for Medical Oncology, European Haematology Association Congress, American Society of Hematology Annual Meeting, and the European School of Haematology International Conference on Multiple Myeloma). Updated database searches were carried out in June 2019.

The company searched two large clinical trials registers in June 2019 (clinicaltrials.gov and WHO ICTRP). Supplementary searches by the company include HTA and drug regulatory agency website searching (NICE, CADTH, Drugs@FDA, and EMA) (page 7 of Appendix D.1.1 of the CS).[3]

In Appendix D of the CS[3] (pages 7-30), the company reported the full and updated literature search strategies, all databases, trial registries, conference abstract and HTA and drug regulatory agency

website searches. The ERG considers that the company's reported search strategies are comprehensive and would retrieve important citations relating to all eligible studies.

3.1.2 Inclusion criteria

The inclusion criteria are generally consistent with the NICE final scope,[6] with three inconsistencies: (1) in the company's systematic review inclusion criteria, there was no requirement for the population to have received lenalidomide and a proteasome inhibitor in a prior line of treatment; (2) the final NICE scope specifies pomalidomide in combination with low-dose dexamethasone and panobinostat in combination with bortezomib and dexamethasone, whereas the company's systematic review inclusion criteria lists additional medication (although the CS specifies that for the purposes of this submission, only IsaPd, Pd and PanVd were eligible for inclusion in the review); (3) the company's systematic review inclusion criteria list additional outcomes to the final NICE scope (time on treatment, treatment free interval, discontinuations, mortality). While not consistent with the stated decision problem, the ERG does not consider these differences to be problematic, as they would broaden rather than narrow the scope of the review, meaning that the relevant papers would still have been identified. Eligibility is restricted to English language publications, which introduces the risk that relevant data not published in the English language may have been missed by the review. It is difficult to estimate the impact of this, however the ERG does not anticipate that any important studies on IsaPd would have been published in another language and therefore missed.

3.1.3 Critique of study selection

Appendix D of the CS[3] states that two reviewers independently undertook record selection, with a third reviewer adjudicating any disagreements. The ERG considers this to be an appropriate and high-quality reviewing method. Full texts of all papers meeting the eligibility criteria in the abstract screening were obtained and screened against the eligibility criteria, although no detail is reported in the CS[3] about the number of reviewers who screened full texts for inclusion, or the process of decision-making. Consequently, the ERG cannot comment on this aspect of study selection. The ERG has screened the titles of the full texts excluded by the company (CS Appendix D, Table 3, page 51),[3] and has examined the full texts of any with potential relevance to the decision problem, and agrees with the exclusion of these texts. Neither the ERG nor clinical advisors to the ERG are aware of any additional studies within the scope of this appraisal.

The PRISMA flow diagram (CS, page 29) and text (CS, page 28)[3] referred to a total of three studies identified that were considered of relevance to the submission, one of which was presented in the PRISMA flow diagram as being 'additional evidence'. In response to clarification questions A1 and A2,[7] the company stated that the three studies considered of relevance to the submission were ICARIA-MM, PANORAMA-1 and PANORAMA-2, and that the single-arm study presented as 'additional

evidence', was PANORAMA-2 and was identified by the company rather than through the process of the systematic review, as the review focused on RCTs.[7] The PANORAMA-2 study was identified by the company reviewing other NICE submissions for RRMM (CS, Appendix K, page 280).[3]

3.1.4 Critique of data extraction

No detail is reported in the CS[3] about the process of data extraction, and thus it is not clear by whom this was done, if it was checked, how any disagreements were resolved, or which fields were extracted. The company's response to clarification question A3[7] indicates that two reviewers independently extracted data, with a third reviewer adjudicating any disagreements. The company's clarification response[7] outlines the fields extracted, and the ERG is satisfied that they are comprehensive.

3.1.5 Critique of quality assessment

The study quality of the ICARIA-MM RCT[4] was assessed using the checklist recommended by NICE for assessing the methodological quality of RCTs; this checklist bears a close resemblance to the Cochrane Risk of Bias tool,[8] which is widely regarded as the most robust tool for the assessment of bias in RCTs. Two reviewers independently assessed the risk of bias and any disagreements were resolved through discussion or by consulting a third reviewer. The ERG considers this to be a robust reviewing method.

No judgement on the overall risk of bias was reported in the CS, and no attempt has been made to integrate the quality assessment into the findings, or to consider the overall impact of the quality of the included study on the results.[3]

Quality assessment of the included study, ICARIA-MM, as undertaken by the company and the ERG, is presented in Section 3.2.3. A quality assessment of the PANORAMA-2 study[9] (see Section 3.2.1) is also presented in Section 3.3.1. The company did not provide a quality assessment of the PANORAMA-2 study in the CS; the ERG have undertaken this using the Newcastle-Ottawa Scale,[10] as it is an appropriate and validated quality assessment tool for non-randomised studies.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Studies included in/excluded from the submission

The CS[3] includes one study that examined the efficacy of IsaPd for treating RRMM – the ICARIA-MM RCT. ICARIA-MM is a pivotal prospective, open-label, multicentre, multinational, randomised parallel group double-arm Phase III study.[4] The CS and the clinical study report (CSR) state that ICARIA-MM was conducted across 102 sites in 24 countries: Australia, Belgium, Canada, Czechia, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Korea, New Zealand, Norway, Poland, Portugal, Russia,

Slovakia, Spain, Sweden, Taiwan, Turkey, UK, and the USA.[3, 11] The number of patients and study centres in the UK is unclear. Forty-five (29.2%) and 45 (29.4%) patients in the IsaPd and Pd arms, respectively, were at 3L, 52 (33.8%) and 58 (37.9%) were at 4L, and 57 (37.0%) and 50 (32.7%) were at 5L+ (CS, Table 9, page 44). The additional study characteristics of ICARIA-MM are presented in the CS, Tables 6 and 7, pages 32 to 38.[3]

Two additional studies have supplied evidence for this appraisal. Study TCD14079 is a Phase 1b non-comparative open-label dose-escalation study, which was undertaken to determine the recommended dose of IsaPd in patients with RRMM. As a non-comparative Phase 1b study, the evidence within Study TCD14079 has been superseded by the ICARIA-MM study,[4] and therefore Study TCD14079 was not used to inform the company's economic model or indirect treatment comparison. However, it has been presented in CS Section B.2.8 (Table 26) and Appendix M.1 for completeness.[3]

The PANORAMA-2 study[9] is a single-arm Phase II study that assesses the safety and efficacy of PanVd, a comparator listed in the final NICE scope,[6] in patients with RRMM who had received at least two prior treatments. The PANORAMA-2 study has been used in the CS (Appendix K, Section K.4.1)[3] to inform the economic model and the indirect comparison with IsaPd (see Sections 3.3 and 3.4).

ICARIA-MM is used in the model for the key comparison of IsaPd vs Pd, whilst a MAIC using ICARIA-MM (IsaPd arm, intention to treat data) and PANORAMA-2 was done for the comparison of IsaPd against PanVd.

3.2.1.1 Patients

Eligibility criteria for the ICARIA-MM study are presented in Tables 6 and 7 of the CS,[3] pages 32 to 38. One key difference between the eligibility criteria for the ICARIA-MM study and the NICE final scope[6] is that patients were excluded from the ICARIA-MM study[4] if they had been treated with anti-CD38 monoclonal antibody and were refractory to this treatment. A clinical advisor to the ERG raised the issue that this study would exclude any patient who had previously taken daratumumab at second line. Daratumumab (in combination with bortezomib and dexamethasone; DVd) is approved through the CDF for second-line treatment for MM. If DVd were to be routinely recommended as a treatment option in second-line, the implication of this exclusion criterion could mean that the ICARIA-MM study would not be directly relevant to future UK RRMM populations. Clinical advice to the ERG commented that IsaPd may be used in later lines post DVd despite both being anti-CD38 monoclonal antibodies, if the patient was not refractory to daratumumab and the patient had received a non-anti-CD38-based treatment inbetween.

A flow diagram of patient flow through the ICARIA-MM study is presented in Figure 12, page 39 of the CS,[3] which was correct at the time of data cut-off (although it is unclear whether this is the 11th of October or the 22nd November 2018; CSR, page 68).[11] Initially, 307 patients were randomised (IsaPd n=154; Pd n=153) and all but two patients in the IsaPd arm and four patients in the Pd arm received the treatment to which they had been allocated.[3] Of these, 100 patients (IsaPd n=65; Pd n=35) were still receiving ongoing treatment. Of the 154 patients who were randomised to IsaPd, 87 (56.5%) withdrew; in the majority of cases (n=66, 42.9%) this was due to disease progression (or death). Eleven (7.1%) withdrew because of adverse events (AEs), one (0.6%) due to poor compliance with the protocol, five (3.2%) due to patient choice and four (2.6%) due to other reasons. Of the 153 patients who were randomised to Pd (the control arm), 114 (74.5%) withdrew; in the majority of cases (n=88, 57.5%) this was due to disease progression (or death). Nineteen (12.4%) withdrew because of adverse events (AEs), six (3.9%) due to patient choice and one (0.7%) due to another reason. A *post hoc* analysis of patients at the fourth-line (4L) of treatment was conducted; there were n=52 patients at 4L in the IsaPd arm and n=58 patients at 4L in the Pd arm.[3]

Demographic and clinical characteristics were comparable between the IsaPd and Pd groups at baseline in both the ITT and 4L populations, with the following exceptions, which the CS notes (CS, Tables 8 and 9, pages 41 to 45): there was a greater proportion of patients aged ≥65 years in the IsaPd than the Pd arm (64.9% vs. 54.2%, respectively; 63.5% vs. 53.4% respectively in the 4L population); a greater proportion of males in the IsaPd than the Pd arm (57.8% vs. 45.8%, respectively; 57.7% vs. 46.6% respectively in the 4L population); and fewer patients from Western Europe in the IsaPd than the Pd arm (35.7% vs. 49.7%, respectively; 36.5% vs. 50.0% respectively in the 4L population), with a greater proportion of patients from Eastern Europe (18.2% vs. 13.1%, respectively; 25.0% vs. 17.2% respectively in the 4L population) and Asia (13.6% vs. 9.8%, respectively; 9.6% vs. 8.6% respectively in the 4L population). A slightly higher proportion of patients in the IsaPd than the Pd arm had impaired renal function at baseline (38.7% vs. 33.8%, respectively; 40.4% vs. 37.5% respectively in the 4L population). Clinical advice received by the ERG suggested that these slight imbalances were unlikely to have impacted on the relative effectiveness of IsaPd. A smaller proportion of patients in the IsaPd than the Pd arm had high-risk chromosomal abnormalities (CA; 15.6% vs. 23.5%, respectively; 15.4% vs. 22.4% respectively in the 4L population); del(17p) and t(4;14) were the most frequent abnormalities. Clinical advice received by the ERG suggested that patients with high-risk CA tend to have a poorer prognosis, which may have been favourable to IsaPd. Although not discussed in the CS,[3] the ERG note that a smaller proportion of patients in the IsaPd than the Pd arm scored 0 on the Eastern Cooperative Oncology Group (ECOG) performance status measure at baseline (35.7% vs. 45.1%, respectively; 40.4% vs. 51.7% respectively in the 4L population), with a greater proportion of patients scoring 1 in the IsaPd arm than the Pd arm (53.9% vs. 44.4%, respectively; 48.1% vs. 39.7% respectively in the 4L population), which may have been unfavourable to IsaPd. The ERG notes that baseline balance or

imbalance is not relevant if a characteristic is not prognostic. However, all stratification factors (i.e. age and lines of therapy) and known prognostic factors should be adjusted for in an analysis of covariance irrespective of baseline balance and their statistical significance. In the case of non-linear models, ignored covariates will produce biased estimates of treatment effect. The company has not generated estimates of treatment effect adjusted for stratification factors and known prognostic factors. Clinical advice received by the ERG suggested that the patient characteristics of the ICARIA-MM study (including the ITT and 4L populations) are broadly reflective of clinical practice in England, albeit being slightly younger and with a slightly lower proportion of black patients. The difference in the average age between patients in the ICARIA-MM study and in England may result in a different treatment effect, although the ERG is unable to comment on whether this would be less or greater for patients in England compared with that estimated in the trial. Clinical advisors to the ERG believed that the lower proportion of black patients would not affect the estimate of treatment efficacy.

3.2.1.2 Intervention

Patients in the IsaPd arm of the ICARIA-MM study received the following treatment combination: isatuximab 10mg/kg IV infusion on days 1, 8, 15 and 22 at Cycle 1, and then on Days 1 and 15 for subsequent cycles; pomalidomide 4mg orally on days 1 to 21 of each 28-day cycle; dexamethasone 40mg (or 20mg if the patient is aged ≥75 years old) orally or IV, on days 1, 8, 15 and 22 of each 28-day cycle. Dose reductions of isatuximab were not permitted, and none were reported (CS, Appendix G, page 118).[3] Permitted and disallowed concomitant treatments are detailed in the CS, Table 6, page 33. The company's clarification response to question A4[7] indicates that the majority (61.2%) of patients in the IsaPd arm of the ICARIA-MM trial received oral dexamethasone, 37.5% received dexamethasone both orally and IV, and 1.3% received dexamethasone via IV administration only. Around half of the 4L patients in the IsaPd arm (50.98%) received oral dexamethasone, 47.06% received both oral and IV dexamethasone, and 1.96% received dexamethasone via IV administration only.

There were [redacted] protocol deviations that were considered to be '*critical or major*' in the IsaPd arm before or during the ICARIA-MM study, and [redacted] in the Pd arm (CSR page 71)[11]. See Section 3.2.3.2 for further details.

3.2.1.3 Comparator

The comparator in the ICARIA-MM study was treatment with Pd, delivered in the following treatment combination: pomalidomide 4mg orally on days 1 to 21 of each 28-day cycle; dexamethasone 40mg (or 20mg if the patient is aged ≥75 years old) orally or IV, on days 1, 8, 15 and 22 of each 28-day cycle. This is identical to the pomalidomide and dexamethasone administration in the IsaPd arm and is consistent with current practice. The ERG considers this to be an appropriate comparator.[12] Permitted and disallowed concomitant treatments were the same as for the IsaPd arm, and are detailed in the CS,

Table 6, page 33.[3] The company's clarification response to question A4[7] indicates that the majority (97.3%) of patients in the Pd arm of the ICARIA-MM trial received oral dexamethasone, with only 2.7% receiving dexamethasone both orally and IV; no patients in the Pd arm received dexamethasone via IV administration only. All 4L patients in the Pd arm received oral dexamethasone only.

3.2.1.4 Outcomes

Table 1 summarises the outcomes listed in the CS.[3] A small number of outcomes presented in the CS[3] were not included in the final NICE scope[6] and are not directly mentioned in the EMA's guideline on the evaluation of anticancer medicinal products.[3, 6, 12]

All efficacy and health-related quality of life (HRQoL) outcome data were analysed using the intention-to-treat (ITT) population, consisting of all randomised patients who gave written informed consent, regardless of whether they were treated or not, analysed according to the treatment group to which they were originally allocated.[3] Outcomes were also analysed *post hoc* within the 4L population, as IsaPd is positioned within the CS as a 4L treatment for RRMM. The company's clarification response question A5[7] indicates that the 4L *post hoc* analysis used data on patients at 4L from the ITT population (rather than the safety population).

Table 1: Summary of outcomes listed in the CS and their relationship to EMA research recommendations, the final NICE scope, and the company's health economic model

Outcome	Recommended by EMA for inclusion in Phase III trials?	In NICE scope?	Used in economic model?	Defined *a priori*?
Primary outcome				
Progression-free survival (PFS) – time from the date of randomisation to the date of first documentation of progressive disease or date of death from any cause	Y	Y	Y	Y
Secondary outcomes				
Overall response rate (ORR) from the date of randomisation to the date of first documentation of progressive disease (as defined by the IRC)	Y	Y	N	Y
Overall survival (OS) – time from the date of randomisation to the date of death from any cause	Y	Y	Y	Y
Time to progression (TTP) from the date of randomisation to the date of first documentation of progressive disease	Could be considered under "alternative endpoints" in the EMA recommendations	Y	Indirectly through PFS	Y
Duration of response (DOR) –from the first IRC determined response to first IRC determined disease progression or death	Could be considered under "alternative endpoints" in the EMA recommendations	Y	N	Y
Best overall response (BOR) – defined by IRC response assessment, from start of treatment until disease progression, death, initiation of further anti-myeloma treatment or cut-off date	Could be considered under ORR in the EMA recommendations	N	N	Y
Time to first response – from randomisation to first IRC determined response (partial response or better)	Could be considered under "alternative endpoints"	N	N	Added per SAP amendment 1
Time to best response –from randomisation to the first occurrence of IRC determined BOR (partial response or better)	Could be considered under "alternative endpoints" in the EMA recommendations	N	N	Y
HRQoL assessed by the electronic questionnaires EORTC-QLQ-C30, EORTC-QLQ-MY20 and EQ-5D-5L	Y	Y	Y (EQ-5D-5L was mapped to EQ-5D-3L)	Y
Treatment-emergent adverse events up to 30 days after last study treatment administration	Y	Y	Y	Y
Minimal residual disease – an exploratory endpoint to determine depth of response at the molecular level (see CSR, page 43)	N	N	N	Y
Time to next treatment	N	Y	Y	N

BOR - best overall response; DOR - duration of response; EMA - European Medicines Agency; EORTC-QLQ-C30 - European Organisation for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire with 30 items; EORTC-QLQ-MY20 - European Organisation for Research and Treatment of Cancer Quality of Life Multiple Myeloma Specific Module with 20 items; EQ-5D-5L – EuroQoL Group 5-dimention 5-Level questionnaire; HRQoL – Health-related quality of life; IMWG - International Myeloma Working Group; IRC - Independent Response Committee; ORR – Overall Response Rate; OS – Overall Survival; PFS – Progression-Free Survival.

Primary outcome

The primary outcome of the ICARIA-MM trial was PFS, assessed from the date of randomisation to the date of first documentation of progressive disease, as determined by the Independent Response Committee (IRC), according to the International Myeloma Working Group (IMWG) criteria using central laboratory results and central review of radiologic imaging, or the date of death from any cause, whichever came first.[3] While OS is arguably the most important outcome of a study, PFS is considered of benefit to patients and can be a feasible primary outcome in this context.[12] For the current appraisal, PFS data from the cut-off date (11th October 2018) were used. Patients without progressive disease or death before the analysis cut-off date were censored at the date of the last valid disease assessment.[11] Assessments were made on Day 1 of each cycle (every 4 weeks), and at the end of treatment (30 days after the last study treatment was administered).[11] The ICARIA-MM study was powered to detect a 40% reduction in the hazard rate between the study arms with 90% power using a one-sided significance level of 2.5%. Assuming an exponential distribution, this would occur when 162 PFS events had been observed.[4] The 162nd PFS event occurred on the 11th of October 2018; therefore, this date was used as the cut-off date for the efficacy analyses, which is the final data cut-off for PFS.[11] While the study was open-label, the CSR (page 30) reports that the IRC performed radiological and central laboratory assessments, on which the disease response evaluations were based, and the IRC was blinded to treatment allocation.[11]

Secondary outcomes

Outcomes listed in the final NICE scope[6] and reported in the CS[3] as secondary outcomes included:

- Overall survival (OS)
- Overall response rate (ORR)
- Time to progression (TTP)
- Duration of response (DOR)
- HRQoL
- Adverse events

Along with PFS, these outcomes form the focus of this report. Data on all other outcomes (see Table 1) are presented in the CS.[3]

EMA research recommendations advise that OS should be considered a secondary outcome in Phase III trials where PFS is the primary outcome, and should demonstrate or show a trend towards superiority.[12]

ORR was defined as the proportion of patients with stringent complete response, complete response, very good partial response and partial response as best overall response and assessed by the IRC using IMWG criteria. This is consistent with EMA recommendations that ORR be documented according to international standards.[12] The EMA also advises that the ITT principle be adhered to in evaluation of ORR. Data from the ITT and 4L populations of the ICARIA-MM study meet this recommendation, as all participants were analysed in the group to which they were allocated.[3] However, the 4L population is a *post hoc* non-stratified population that does not have the protection of the randomisation when making comparisons between treatments.

TTP and DOR might be considered among the "*alternative endpoints*" suggested by the EMA research recommendations[12] as acceptable, and Davis *et al.*[13] recommend TTP as a simple and comprehensive endpoint for Phase II to IV clinical studies of pharmaceutical agents. DOR was defined as the time from the date of the first IRC-determined response to the date of first IRC-determined disease progression or death, whichever occurred first.

HRQoL was assessed in the ICARIA-MM study by the use of the European Organisation for Research and Treatment of Cancer Quality of Life Cancer Specific Questionnaire with 30 items (EORTC-QLQ-C30), European Organisation for Research and Treatment of Cancer Quality of Life Multiple Myeloma Specific Module with 20 items (EORTC-QLQ-MY20) and EuroQoL Group self-report questionnaire with 5 dimensions 5-level (EQ-5D-5L) questionnaires, prior to study-related activities on day 1 of each treatment cycle, at the end of treatment visit and 60 days (±5 days) after the last study treatment administration. According to clinical advice received by the ERG, such measures would not be routinely used in clinical practice (HRQoL would not be formally measured in real-world practice). However, the EORTC-QLQ-C30 is a commonly-used questionnaire for research with myeloma patients. The results for the cognitive, social and emotional functioning subscales were not in the CS; the company have submitted these in their response to clarification question A11.[7] Clinical advice received by the ERG suggested that the global health status (GHS) may not be a reliable indicator of perceived health/HRQoL as people find it difficult to consider their health and wellbeing in such global terms, that perceived health varies over the course of RRMM and that there could be high unmet needs. The EMA research recommendations[12] and EMA guidance on measuring HRQoL in oncology[14] recommend the use of a validated cancer-specific HRQoL measure where possible (although they do not specify which instrument should be used), and as such, the EORTC-QLQ-C30 fulfils this criterion.

All adverse events (AEs) reported in the ICARIA-MM study were classified as treatment-emergent adverse events (TEAEs) and were recorded from the time of informed consent to 30 days following the last administration of IsaPd or Pd.[3] These were defined as AEs that "*developed, worsened (according to the investigator opinion) or became serious during the TEAE period*" (CSR, page 44).[11] The method

of measuring AEs was not given in the CS,[3] although the CSR (page 44)[11] reported that all AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. According to the CS (page 46),[3] the safety population consisted of all patients from the ITT population who received at least one dose or part-dose of their randomised treatment (IsaPd or Pd). Patients were analysed according to the treatment group to which they were originally allocated.[3] No definition of what constituted a serious adverse event (SAE) is presented in the CS[3] or CSR.[11] However, the clinicaltrials.gov record states that an SAE constituted "*any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a medically important event*".[15]

3.2.1.5 Study design

The ICARIA-MM study was a prospective, open-label, multi-centre, multinational, parallel-group Phase III RCT, where eligible patients (n=307) were randomised to IsaPd or Pd. Patients were randomised at a 1:1 ratio using an interactive response technology (IRT) system. Randomisation was stratified by age (<75 years vs. ≥75 years) and number of previous lines of therapy (2 or 3 vs. >3) (CS, Table 6, page 32).[3] The ERG considers that the study design could have been more rigorous, as the ICARIA-MM trial was open-label and the EMA evaluation guidelines[12] recommend the use of double-blind Phase III RCTs that compare against the current standard of care for establishing the benefit-risk profile of a medicinal product.

Post hoc analyses were conducted and reported in the CS for a subgroup of patients in the ICARIA-MM study at 4L of treatment, relating to selected outcomes.[3] The ERG's appraisal focuses on evidence from the 4L *post hoc* analyses, as this is the most relevant patient population from the ICARIA-MM study based on the proposed positioning by the company and these data have informed the company's health economic model. However, the ERG has some reservations with this *post hoc* approach, as it was not a stratified group and does not have the protection of the randomisation when making comparisons between treatments.[16] The selection of the *post hoc* population was based on consideration of the proposed position of IsaPd in the RRMM treatment pathway. However, as baseline demographics and clinical characteristics were similar between the 4L patients and the full population and clinicians did not believe the relative efficacy to differ by line of treatment the analyses were believed suitable for decision making.

3.2.1.6 Ongoing studies

The ICARIA-MM study is currently ongoing, with efficacy data from the 11th of October 2018 cut-off and safety data from the 22nd of November 2018 cut-off used in the CS.[3] The PFS data from the

ICARIA-MM study were mature. However, OS data are less mature. The final analysis of OS will occur after ≥220 deaths have been observed, which is expected in Q2 2021 (CS, page 91).[3]

An additional study, the IKEMA study, is reported in the CS (page 87)[3] as being currently ongoing. However, as the study compares isatuximab, carfilzomib and dexamethasone with carfilzomib and dexamethasone in patients with RRMM, the ERG does not consider this relevant to the current decision problem.

3.2.2 Details of relevant studies not included in the submission

The ERG is confident that the ICARIA-MM study is the only relevant study in this patient population, that the PANORAMA-1[17, 18] and PANORAMA-2[9] studies are potentially the only relevant comparator studies for the comparison with IsaPd to PanVd (see Section 3.3), and that no relevant studies have been omitted from the CS.[3] The methods employed by the company and a critique of these methods are provided in Section 3.4.

3.2.3 Summary and critique of the company's quality assessment

3.2.3.1 Critical appraisal of study quality of ICARIA-MM

The company provided a critical appraisal of the validity of the ICARIA-MM study[4] using the checklist recommended by NICE, which bears a close resemblance to the Cochrane Risk of Bias tool.[19] A summary of the risk of bias in the ICARIA-MM study undertaken by the company alongside the ERG's independent quality assessment is presented in Table 2. The ERG has also specified the level of risk of bias for each criterion.

The company's critical appraisal and the ERG's critical appraisal of the ICARIA-MM study[4] were similar. The ERG concludes that there is a moderate risk of bias for the ICARIA-MM study; the company did not provide a summary appraisal of risk of bias. Both the company and the ERG agree that there were some differences in baseline characteristics between study arms, although the relevance of these depends on whether the characteristics are prognostic; a correct analysis includes all stratification factors and all observed prognostic variables irrespective of baseline balance. The study was open-label, which may have introduced measurement bias; and a greater proportion of patients in the Pd group than the IsaPd group withdrew due to disease progression (whether this was expected or not was unclear from the CS).[3]

Details of the PANORAMA-2 study quality assessment are reported in Section 3.3.

Table 2: Company and ERG quality assessment of ICARIA-MM (adapted from CS, Appendix K, Table 46)

Quality assessment criterion question	Company quality assessment (yes/no/not clear/NA)		ERG quality assessment (yes/no/not clear/NA)	
	Grade	Explanation	Grade	Explanation
Was randomisation carried out appropriately?	Yes	Patients were randomised according to an interactive response system and stratified according to age and prior therapy.	Yes	Patients were randomised using an IRT system, stratified by age and previous lines of therapy.
Was the concealment of treatment allocation adequate?	Yes	A centralised interactive response system was used to allocate patients.	Yes	Patients were allocated using a centralised IRT system.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Unclear	Authors stated that the baseline characteristics of the two groups were generally well balanced with the exception of gender and geographical region, but no statistical analysis conducted.	Unclear	Baseline characteristics differed on some demographic and disease-related characteristics.
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	Open-label. Disease response assessments were evaluated based on radiological and central laboratory assessments by the IRC which was blinded to treatment group allocation.	No	The study was open-label. The IRC (which was blinded to treatment allocation) undertook the radiological and central laboratory assessments, on which the disease response evaluations were based.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Unclear	Higher rate of discontinuation due to disease progression in the Pd group: 57.5% vs 42.9% in the IsaPd group.	Unclear	A greater proportion of patients in the Pd group (57.5%) than in the IsaPd group (42.9%) withdrew due to disease progression. It is unclear whether this was unexpected or not, although this was explained in terms of the efficacy of IsaPd.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	There was no evidence of selective reporting. All specified outcomes were reported.	No	There are no outcome measures specified in the protocol (including previous versions) that have not been reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The ITT analysis was reported and included all patients randomised for efficacy outcomes. Details of patient censoring also provided.	Yes	Analysis using the ITT population was reported for all efficacy outcomes, and this included all randomised patients.

IRC – Independent Response Committee; IRT – interactive response technology; ITT – intention to treat;

3.2.3.2 Protocol deviations

The CSR[11] reports a total of [redacted] critical or major protocol deviations in the IsaPd arm and [redacted] in the Pd arm. A comparable proportion of patients in the Pd arm than the IsaPd arm ([redacted] vs. [redacted]) had progressed after 60 days of the last dose of the immediate previous line/regimen. [redacted] in the IsaPd arm ([redacted]) had prior exposure to pomalidomide and [redacted] in the IsaPd arm ([redacted]) had been diagnosed or treated for another malignancy within three years prior to randomisation. In the Pd arm, [redacted] had an absolute neutrophil count < 900, [redacted] had a major procedure or major surgery within 14 days prior to study initiation, [redacted], and [redacted] did not have evidence of measurable disease (M-protein in serum < 0.5g/dL and urine < 200mg/24 hours). The ERG considers these protocol deviations unlikely to impact on the conclusions of the ICARIA-MM study.

Another consideration is the difference in pomalidomide exposure between the IsaPd and Pd arms, which may impact on trial outcomes. The mean relative dose intensity (RDI) of pomalidomide was [redacted] (SD [redacted]) in the IsaPd arm, and [redacted] (SD [redacted]) in the Pd arm (CSR, Table 45, page 131).[11] As ICARIA-MM was open-label and pomalidomide was taken orally, it is possible that patients in the Pd arm took a higher dose of pomalidomide to compensate for not receiving isatuximab.

3.2.4 Summary and critique of results

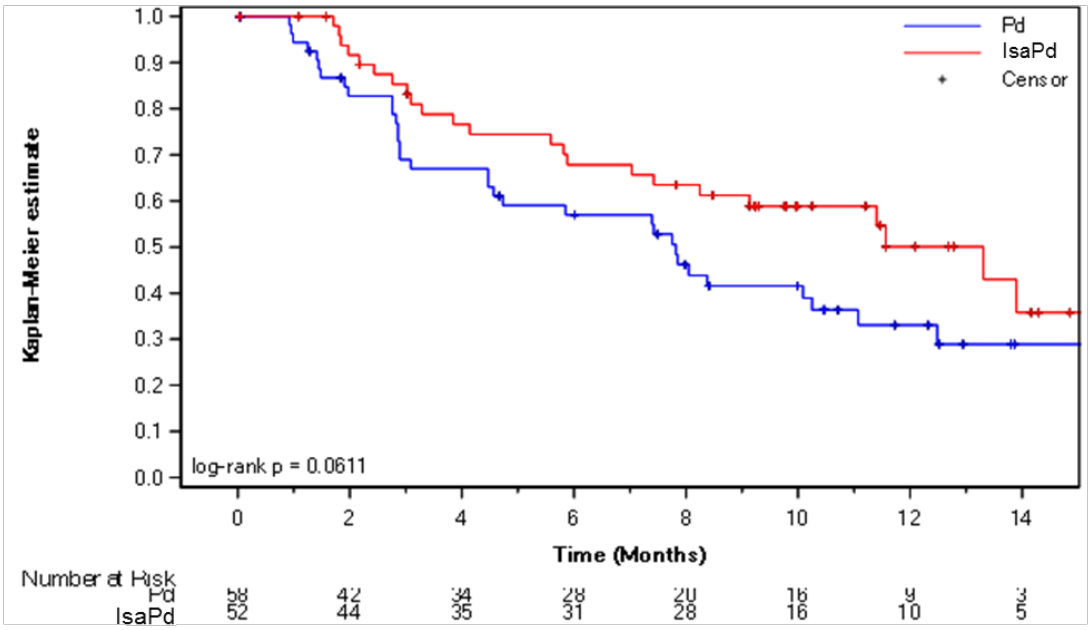
The data cut-off date for the efficacy analyses was the 11th of October 2018, and the cut-off date for other analyses (safety, disposition, and baseline characteristics) was the 22nd of November 2018. As the 162nd PFS event occurred on 11 October 2018, this date was used as the cut-off date for the efficacy analyses and a last patient visit of 22 November 2018 was selected (CSR, page 68).[11] The median duration of follow-up was reported in the CS as being 11.56 and 11.73 (for OS) (CS, page 57), and the recently published Attal *et al*. paper gives the median duration of follow-up as being 11.6 months (IQR 10.1-13.9) at data cut-off for the efficacy analyses among the trial population.[4] The mean (SD) duration of exposure was 37.81 (20.29) and 29.33 (20.57) weeks for the IsaPd and Pd arms, respectively, and the median (range) duration of exposure was 41.00 (1.3, 76.7) and 24.00 (1.0, 73.7) weeks for the IsaPd and Pd arms, respectively.

3.2.4.1 PFS (primary endpoint)

PFS was assessed after 162 patients (of 309) had progressed or died, which included 56 PFS events in the 4L population (n=110). In the 4L population, the median PFS was greater in the IsaPd arm (13.31 months [95% CI: 7.425, not calculable]) than in the Pd arm (7.82 [95% CI: 4.468, 11.072])

(stratified (by age) Log-Rank test *p*-value vs Pd: 0.0611), and the stratified (by age) hazard ratio (HR) was 0.598 (95%: CI 0.348, 1.030), which the CS states represents a 40.2% risk reduction of disease progression or death in favour of IsaPd compared with Pd (Figure 2).[3] Twenty-nine (55.8%) and 25 (43.1%) of 4L population patients in the IsaPd and Pd arms, respectively, had not had a PFS event at data cut-off.

Figure 2: Kaplan-Meier curves for PFS by treatment group, 4L population (adapted from CS, Figure 14, page 53)



Cut-off date: 11th October 2018.

Log-rank p-value stratified by age (<75 years vs ≥75 years) according to IRT. One-sided significance level: 0.025.

Abbreviations: IRT, interactive response technology; IsaPd, isatuximab, pomalidomide, low-dose dexamethasone; ITT, intention-to-treat; MM, multiple myeloma; Pd, pomalidomide, low-dose dexamethasone; PFS, progression free survival.

3.2.4.2 ORR

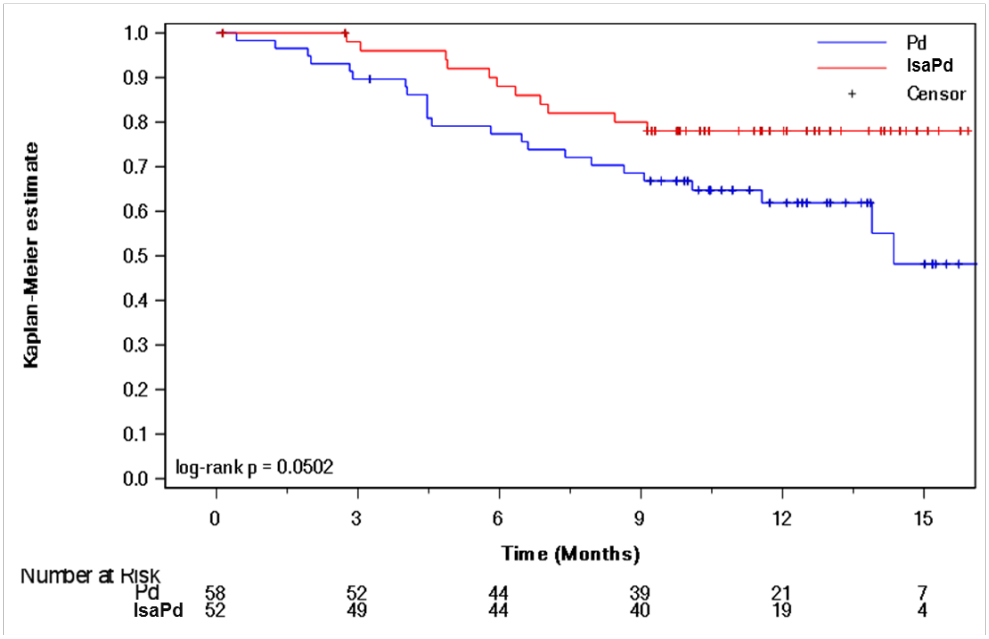
The ORR for patients in the 4L population was higher in the IsaPd arm (53.8%) than in the Pd arm (46.6%), although this difference was not statistically significant (*p*=0.3991). Similarly, a (non-statistically significantly) greater proportion of participants in the IsaPd arm had a very good partial response or better (26.9% vs. 15.5%; *p*=0.1552, for the IsaPd and Pd arms, respectively) and a complete response (3.4% vs. 1.9% for the IsaPd and Pd arms, respectively (*p*-value not reported). The CS states that "*the proportion of patients with CR in the IsaPd was likely to be underestimated; isatuximab interferes with M-protein measurements in the immunofixation test*" and thus it was possible that some patients recorded as having a near-complete response (i.e. a response on all measures except the immunofixation test) may have in fact had a complete response. Clinical advice

received by the ERG suggested that this was possible, although this phenomenon would be unlikely to have a clinically relevant impact on this outcome variable. Data for the ITT population of ICARIA-MM are reported in the CS, (pages 54-55).[3]

3.2.4.3 OS

Interim data and analyses were reported in the CS for OS. The interim analysis of OS for IsaPd and Pd was conducted using a log-rank test, with a one-side significance level of 0.0008 (determined by using O'Brien and Fleming α-spending function) (CS, page 57). Among the ITT population, 99 death events (43 in the IsaPd arm and 56 in the Pd arm) were reported at data cut-off; this represented 45% of the target of 220 events required to achieve 80% statistical power to detect a 31.5% reduction in hazards at a one-sided significance level of 2.5%. Final OS analyses are planned once 220 deaths have been observed (anticipated in Q2 2021). In the 4L population, there were 34 death events; 11 (21.2%) in the IsaPd arm and 23 (39.7%) in the Pd arm at data cut-off; 69% of 4L patients were still alive at a median follow-up of 11.6 months and were censored. A trend for greater median OS in the IsaPd arm (compared with the Pd arm) was reported in the CS, with a median OS of 14.36 months (95%: CI 11.57, not calculable) in the Pd arm whilst the median OS had not been reached in the IsaPd arm (stratified HR 0.49 [95% CI 0.24, 1.02], *p*=0.0502) (Figure 3; CS, pages 60-61).

Figure 3: Kaplan-Meier curves for OS† by treatment group, 4L population (adapted from CS, Figure 16, page 62)



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

OS may have been impacted by the subsequent use of daratumumab which does not reflect current clinical pathways in England. The CS[3] reported that 3.8% and 27.6% of 4L patients in the IsaPd and Pd arms, respectively, had received daratumumab as subsequent therapy at the cut-off date, which increased to values of 7.1% and 38.1% given longer follow-up to July 2019 (Sanofi, data on file)). Subsequent use of daratumumab in patients who progress at 4L will potentially be inconsistent with the current clinical management pathway for RRMM in England if isatuximab is approved for use at 4L. Therefore, this may compromise the generalisability of the ICARIA-MM study results to the context of the NHS in England. The CS urges caution in interpreting the longer-term OS data, considering the high levels of censoring and subsequent therapy, particularly daratumumab.[3]

3.2.4.4 TTP

The median TTP was greater in the IsaPd arm of the 4L population (13.31 months [95% CI: 8.25, not calculable]) compared with the Pd arm (8.05 months [95% CI: 5.85, not calculable]; HR and *p*-value not reported). Median TTP for the ITT population is reported in the CS, Table 20.[3]

3.2.4.5 DOR

The median DOR was not calculable for both the IsaPd and Pd arms in the 4L population. Although the stratified HR (0.63 [95% CI: 0.22, 1.77]; *p*-value not reported) favoured IsaPd over Pd there was uncertainty regarding the direction and magnitude of effect. Median DOR and stratified HR for the ITT population is reported in the CS, Table 20.[3]

3.2.4.6 HRQoL

Among the 4L patients, HRQoL assessed using the EQ-5D-5L health state utility index and visual analogue scale was similar between groups and worsened slightly over time, although slightly more so in the IsaPd arm than the Pd arm. The company urge caution in interpreting the results due to a small sample size and absence of significance testing (CS, page 74).

There was little difference between IsaPd and Pd in the 4L population on EORTC QLQ-C30 score (representing scores in physical functioning, role functioning, cognitive functioning, emotional functioning and social functioning subscales) across the treatment cycles, with both treatments having a reduced HRQoL at the end of treatment, presumably due to disease progression (CS, Figure 18, page 72).[3] The company have submitted results for the cognitive, social and emotional functioning subscales in their response to clarification question A11,[7] and the results are similar for these subscales.

Results from the QLQ-MY20 were not reported for the 4L population. For the ITT population, the CS reports that there was no clinically meaningful change from baseline in the body image, future perspective, disease symptoms, and side effects scores (page 71).

3.2.4.7 Safety and tolerability

IsaPd appears to be generally well tolerated. At 4L, a greater proportion of patients in the IsaPd arm than the Pd arm experienced grade ≥3 TEAEs (84.3% vs 69.0%, respectively) and treatment-emergent serious adverse events (64.7% vs 53.4%, respectively). However, fewer 4L patients in the IsaPd than the Pd arm had fatal events (7.8% vs 8.6%, respectively) or discontinued treatment due to a TEAE (7.2% vs 17.2%, respectively). An overview of TEAE rates in the 4L population is provided in the CS, Table 28, and rates of specific TEAEs by system organ class for the safety population are provided in the CS, Table 30.[3]

3.2.4.8 Subgroups

The company proposes that IsaPd would be used as a 4L treatment, which represents a known subgroup of the broader marketing authorisation. As such, the company has provided data on this subgroup. Further discussion on subgroups are provided in Sections B2.6.1 and B2.7 of the CS. It is reported that "*Pre-specified subgroup analyses demonstrated a positive treatment effect with IsaPd vs Pd (HR values ranging from 0.479 to 0.827) in all subgroups considered, consistent with the overall PFS analysis. In addition, the analyses showed no significant interaction at the 10% alpha level for treatment arms vs stratification factors, treatment arms vs demographic characteristics, or treatment arms vs patients' baseline characteristics, indicating an overall consistent treatment effect across those subgroups.*"[3]

The company performed subgroup analyses with respect to 12 potential prognostic factors and/or treatment effect modifiers in addition to subgroup analyses of the two stratification factors (age and lines of therapy). Although this approach to assessing differential treatment effects is common, it does have limitations: assessing treatments effects of a subgroup assumes there is no residual heterogeneity of treatment effect within the subgroup; when treatment interacts with factors not used in forming the subgroups, or when the subgrouping variable interacts with an omitted factor, the subgroup treatment effect may be misleading; constructing subgroups from a factor that is continuous assumes that there is a discontinuous treatment effect at the cut-off(s), which is unrealistic. Assessing differential treatment effects is best done through formal interactions tests. As before, the ERG notes that all stratification factors and known prognostic factors should be adjusted for in an analysis of covariance irrespective of baseline balance and their statistical significance, and that unadjusted estimate of treatment effect are biased. The company's approach to estimating the effect of individual covariates should have simultaneously adjusted for stratification factors. Furthermore, the company summarised the results of their subgroup analysis by providing the minimum and maximum hazard ratios but did not include confidence intervals for them. Nevertheless, in spite of the claim by the company that the hazard ratios for the effect of treatment in all subgroups was consistent with the overall PFS analysis, the actual estimates were quite different. The impact of this on absolute estimates of PFS for patients treated with IsaPd would depend on the risk of PFS for patients treated with Pd.

In addition, the company conducted a multivariable analysis and identified variables to include in the multivariable regression model using stepwise methods. The ERG has concerns with the use of stepwise methods, including: R^2 values are biased upwards, F statistics do not have the claimed distribution, standard errors of parameter estimates are too small, p-values are too low because of multiple comparisons and it is not clear how they should be adjusted, parameter estimates are biased away from the null value, and collinearity problems are exacerbated. Furthermore, the approach used by the company failed to take account of what is already known, including that age and lines of therapy are prognostic factors. In clarification question A13,[7] the ERG asked the company to re-run the multivariable regression analysis leaving in the model the stratification factors and any known prognostic factors irrespective of their statistical significance and baseline balance; to include other potential prognostic factors using criteria other than simply statistical significance, including the magnitude of effect and expert opinion; and to include covariates that are continuous variables (such as age) as continuous variables and assess their relevance using appropriate non-linear relationships. In response, the company simply provided a model with all covariates included and did not assess any potential differential treatment effects (Response to clarification questions,[7] Table 6). Although, as expected, the adjusted treatment effect is greater than the unadjusted treatment effect, it is not clear whether a reduced model would be more appropriate or if interaction terms with treatment should be included.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The PANORAMA-2 study[9] is a single-arm Phase II study that assesses the safety and efficacy of PanVd, a comparator listed in the final NICE scope,[6] in patients with RRMM who had received at least two prior treatments. The PANORAMA-2 study has been used in the CS (Appendix K, Section K.4.1) to inform the comparison of IsaPd against PanVd (see Section 3.1.6) using a MAIC. While the inclusion criteria based on the number of lines was comparable in PANORAMA- 2 and ICARIA-MM, this was not the same as the target population (4L). Patients were adults with relapsed and bortezomib-refractory MM who had received at least two prior lines of therapy (median 4 prior lines, range 2-11).[9] The treatment schedule and baseline characteristics are reported in the Richardson *et al*. publication,[9] and the baseline characteristics of the ICARIA-MM and PANORAMA-2 studies are compared in Table 3.

Table 3: Comparison of baseline characteristics of ICARIA-MM and PANORAMA-2 (adapted from CS, Appendix K, Table 42, page 286)

Characteristic	ICARIA-MM[4]		PANORAMA-2[9]
	IsaPd (n=154)	Pd (n=153)	PanVd (n=55)
Median age (range), years	68 (36 to 83)	66 (41 to 86)	61(41 to 88)
Gender n (%) male	89 (57.8)	70 (45.8)	29 (52.7)
Ethnicity n (%)	White: 118 (76.6) Asian: 12 (13.6) Black or African American: 1 (0.6) Native Hawaiian or other pacific island: 2 (1.3) Unknown: 12 (7.8)	White: 126 (82.4) Asian: (15 (9.8) Black or African American: 3 (2) Native Hawaiian or other pacific island: 1 (0.7) Unknown: 8 (5.2)	NR
Mean weight (SD or range), kg	NR	NR	NR
ECOG performance status n (%)	ECOG 0: 55 (35.7) ECOG 1: 83 (53.9) ECOG 2: 16 (10.4)	ECOG 0: 69 (45.1) ECOG 1: 68 (44.4) ECOG 2: 16 (10.5)	ECOG 0: 26 (47.3) ECOG 1: 25 (45.5) ECOG 2: 4 (7.3)
Time since diagnosis Median years (range)	4.5 (0.6- 18.4)	4.1 (0.5- 20.5)	4.56 (0.6 to 22.0)
ISS disease stage n (%)	I: 36 (23.4)) II: 49 (31.8) III: 42 (27.3) Unknown: 27 (17.5)	I: 41 (26.8) II: 48 (31.4) III: 44 (28.8)) Unknown: 20 (13.2)	I: 18 (32.7) II: 23 (41.8) III: 13 (23.6) Missing: 1 (1.8)
Cytogenetic features n (%)	Del17p, t(4;14) or t(14;16) Absent: 80 (52.3) Present: 33 (21.6) Unknown: 33 (21.6)	Del17p, t(4;14) or t(14;16) Absent: 80 (52.3) Present: 33 (21.6) Unknown: 33 (21.6)	FISH, n (%) Normal: 2 (3.6) Any abnormality: 35 (63.6) del17p, t(4;14), or t(14;16): 14 (25.5) del13q: 5 (9.1)

Characteristic	ICARIA-MM[4]		PANORAMA-2[9]
	IsaPd (n=154)	Pd (n=153)	PanVd (n=55)
			t(11;14): 14 (25.5) 3+: 1 (1.8)
Lab tests Serum LDH levels Albumin levels Renal function (creatinine levels [mL/min]))	 ≤ULN: 106 (68.8) NR	 ≤ULN: 1062 (66.7) NR	 NR Median: 3.69 g/L (30.6 to 48.9) NR
Number of prior therapies Median (range)	3 (2 to 11)	3 (2 to 10)	4 (2 to 11)
Prior autologous stem cell transplant n (%)	83 (53.9)[a]	90 (58.8)[a]	31 (56.4)[b]
Refractory to lenalidomide n (%)	144 (93.5)[c]	140 (91.5)[c]	Not identified by the ERG

[a] *Data from ICARIA-MM CSR (Table 21, page 86)[11]*
[b] *Data from Richardson et al. 2013[9]*
[c] *Data from CS (Table 9, page 44)[3]*
Abbreviations: ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; Isa-Pd, isatuximab+ pomalidomide+ dexamethasone; ISS, International Staging System; LDH, lactate dehydrogenase; NR, not reported; PanVd, panobinostat+ bortezomib+ dexamethasone; Pd, pomalidomide+ dexamethasone; SD, standard deviation

3.3.1 Critical appraisal of study quality of PANORAMA-2

Table 4 presents the quality assessment of the PANORAMA-2 study[9] undertaken by the ERG, based on the Newcastle-Ottawa scale.[10] No quality assessment of the PANORAMA-2 study was presented in the CS.[3]

Table 4: ERG quality assessment for PANORAMA-2 using the Newcastle-Ottawa Scale

Quality assessment question	ERG's quality assessment
Representativeness of the exposed cohort	Unclear
Selection of the non-exposed cohort	N/A (single-arm study)
Ascertainment of exposure	Patients were administered panobinostat, bortezomib and dexamethasone as a study treatment intervention. Administration was monitored.
Demonstration that outcome of interest was not present at start of study	The primary outcome was overall response rate, which could not have been present at baseline.
Comparability of cohorts on the basis of the design or analysis	N/A
Assessment of outcome	Standard clinician-assessed outcome measurements were used, open-label
Was follow-up long enough for outcomes to occur?	Patients were assessed for up to two years, which is sufficient for outcomes to occur
Adequacy of follow up of cohorts	Seven of the 55 patients entered phase 2 of treatment and remained on treatment at the data cut-off. Discontinuations and withdrawals were accounted for; however, attrition was high.
Stars total	**3**

The ERG has rated the PANORAMA-2 study[9] moderate to poor in terms of study quality. The main source of bias is the unblinded nature of the outcome assessment.

3.4 Description and critique of the indirect comparison and/or multiple treatment comparison

The company undertook an exploratory analysis of IsaPd compared with PanVd "*in order to meet the requirements of the scope*" using a MAIC as IsaPd and PanVd were not part of a connected network of evidence.

Initially, the company assessed whether it was feasible to perform a network meta-analysis (NMA) depending on the similarity of the studies in each network against the following criteria: the quality of the methods employed in conducting randomised trials; confounding factors in relation to participant populations; confounding factors in relation to circumstances, and similarity of treatments (common reference and interventions).

The company defined the following outcomes as treatment effect modifiers: age; sex; ethnicity; weight; stage or duration of disease; ECOG performance score; cytogenetic risk group; co-existing disease and concomitant treatments; prior therapies; location; setting; and date of studies.

Three studies were considered relevant with respect to this comparison: ICARIA-MM,[4] PANORAMA-1,[20] and PANORAMA-2.[9] ICARIA-MM compared IsaPd against Pd in adult patients who had received at least 2 prior lines of treatment. PANORAMA-1 compared PanVd against placebo in patients who had received 1-3 prior lines of treatment, although data from the subgroup of patients who had received 2 prior lines of treatment was available. PANORAMA-2 was a single arm study of PanVd in patients who received 2 or more prior lines of treatment. Hence, the studies did not form a network of evidence.

The company assessed the consistency of the PanVd PFS data across the PANORAMA-1 and PANORAMA-2 studies using the Kaplan-Meier (KM) estimates at 6 and 12 months, estimating the HR from a Cox proportional hazards model, and a Mantel-Haenszel test. The ERG considers this unnecessary on the basis that heterogeneity is expected with respect to treatment arms across studies and it is only the relative treatment effect within studies, on some suitable scale, that is additive across studies. Furthermore, absence of evidence of heterogeneity with respect to treatment arms across studies would not be considered by the ERG sufficient justification to assume that the studies are estimating the same parameter of interest. However, the company concluded that the PanVd arms within PANORAMA-1[20] and PANORAMA-2[9] were estimating different parameters and excluded PANORAMA-1 from further consideration on the basis of the number and types of prior treatments received. An assessment of the effect of IsaPd versus PanVd on PFS was conducted using an MAIC of IsaPd from the ICARIA-MM study[4] and PanVd from the PANORAMA-2 study.[9] The comparison between treatments is in a population of patients defined by the PANORAMA-2 study rather than with respect to the target population (i.e. 4L). See Table 3 for details of the PANORAMA-2 study.

In Section K.4.4 of the CS, the company stated that "*OS data were not sufficiently mature for ICARIA-MM and not available for PANORAMA-1 (Table 40) [of the CS]. Furthermore, it was not possible to compare ORR as the trials used different response definitions (Table 41) [of the CS]. Therefore, these outcomes were not included in the MAIC.*"[3] In practice, all three outcomes were analysed.

The company applied the MAIC using individual patient data from ICARIA-MM and using aggregate data from PANORAMA-2. In the matching process the effective sample size for ICARIA-MM was reduced to 91. The MAIC was then used to obtain a HR for PanVd compared to IsaPd which was applied to the underlying survivor functions used for the IsaPd group used in the comparison of IsaPd and Pd.

3.4.1 Progression-free survival

The company included potential or known prognostic factors and/or treatment effect modifiers as covariates in its MAIC model in order to re-weight the PFS data from the ICARIA-MM[4] IsaPd arm to match the distribution of patient characteristics of the PanVd arm of the PANORAMA-2.[9] The following covariates were used: age (median); ECOG performance score; gender; the presence of one

of Del17p, t(4;14) or t(14;16); International Staging System (ISS) stage at study entry; number of prior regimens (median); previous stem cell transplant; time since diagnosis (median); refractory to lenalidomide. It is not clear whether these represent all relevant prognostic factors and/or treatment effect modifiers.

The company fitted various parametric models to the weighted IsaPd and unweighted PanVd data separately to each treatment arm and with a covariate representing a treatment effect. The company assessed the proportional hazards assumption based on whether the two treatment arms on the log cumulative hazard plot versus log time are approximately parallel, whether the Schoenfeld residuals show a random pattern centred on zero, and whether a regression line fitted through the data has a non-statistically significant slope. The ERG believes that the appropriate basis for assessing whether hazards are proportional is to plot the log cumulative hazard against time not against log (time)[21] which is presented in Figure 19A, Appendix K.4 of the CS.[3] Section K.4.5.3.1 of the CS[3] states that "*the test of the linearity of the Schoenfeld residuals is not statistically significant, suggesting that the assumption of proportionality may be appropriate for this comparison.*" However, in the same section, the CS states that "*the test of the linearity of the Schoenfeld residuals is statistically significant, suggesting that a PH distribution (e.g. exponential, Weibull, Gompertz) may be inappropriate.*" The ERG is uncertain regarding which sentence is correct.

Not all models considered were proportional hazards models (e.g. the lognormal and log-logistic distributions are acceleration failure models), which further negates any discussion regarding proportional hazards. Figure 18B in Appendix K.4 of the CS[3] suggests that the hazard for IsaPd is relatively constant over at least the first 12 months, whereas the hazard for PanVd appears to increase over the first 12 months at least. Nevertheless, the ERG does not consider that an assessment of proportional hazards (or acceleration failure) is relevant in the context of an economic evaluation. At best this is a modelling assumption that is not necessary to make unless there is a clear clinical rationale for doing so; absence of evidence against a proportional hazards (or acceleration failure) assumption is not evidence to support a proportional hazards (or acceleration failure) assumption.

The company estimated that the HR from the Cox proportional hazards model for IsaPd compared with PanVd was 0.369 (95% CI 0.259 to 0.526) favouring IsaPd but stated that "*It should be noted that the test of the Schoenfeld residuals was statistically significant suggesting that the PH assumption may be invalid. As the HR for IsaPd vs PanVd was diminishing (benefits increasing) over time (see figure above), the estimated HR may be a reasonable estimate of the average HR during the period of observation but may underestimate the benefits of IsaPd in the long-term.*"

The ERG is concerned with the way the survival functions for each of IsaPd and PanVd were generated. The company generated the IsaPd survival function using a log normal (acceleration failure) model fitted to the 4L subgroup of the ICARIA-MM study and generated the PanVd survival function by imposing a HR from a Cox proportional hazards model of the MAIC-adjusted data. As Guyot *et al*.[22] wrote, "*from a statistical point of view, the Cox hazard ratio will not have the same numerical value as a hazard ratio that would be estimated by fitting the parametric model to both arms. Yet, if we believe that the parametric model correctly represents the standard treatment effect and we accept proportional hazards, then there is no reason to not use the parametric model to estimate the relative treatment effect. Second, overlaying the hazard ratio from one analysis onto a baseline arm from a different analysis will overstate the uncertainty in the analysis because the covariation between baseline and treatment effect that would be expressed in a single coherent analysis is lost*". Furthermore, while it may be reasonable to assume that the treatment effect is unaffected by the lines of treatment, the lognormal distribution is not a proportional hazards model and the combination of a hazard ratio and a lognormal model is inappropriate.

It is unclear to the ERG what is meant by restricted cubic spline Weibull, lognormal and log-logistic models. Weibull, lognormal and log-logistic models can be parameterised using a restricted cubic spline approach depending on the link function used and by including no additional knots. Figure 19B in Appendix K.4 of the CS[3] appears to recognise this but there is no formal discussion regarding the different model assumptions.

Figure 21 in Appendix K.4 presents Bayesian Information Criterion (BIC) statistics for the relative goodness-of-fit of each model to the observed data. However, the ERG is not confident with using these as the basis for model comparison in this submission. In particular, the ERG is concerned because the company states that "*The restricted generalised gamma is the best fitting distribution based on the Bayesian Information Criterion (BIC) statistic, however, this distribution failed to converge and should be disregarded*."[3] The issue is likely to be the way the treatment effect was defined in the three-parameter generalised gamma distribution and the scale on which the treatment effect was estimated.

The company stated that "*Separate HRs for TTD or PFS on treatment could not be computed because the PANORAMA-2 trial did not report KM curves for these outcomes and PFS is the closest proxy outcome available. HRs for PFS were therefore used for PFS, PFS on treatment, and TTD."*[3]

3.4.2 Overall survival

Despite stating in Section K.4.4 of the CS that OS data were not sufficiently mature, the company presented results of a MAIC for OS in Section K.4.5.3.2 of the CS.[3] As with PFS, the company estimated the baseline survival function for IsaPd with respect to the 4L subgroup of the ICARIA-MM study and

estimated relative treatment effect using a Cox proportional hazards model of the MAIC adjusted data. The company considered a lognormal distribution (an acceleration failure model) to provide the best representation of the observed data while also concluding that it was reasonable to assume that the hazards for IsaPd and PanVd were proportional. Furthermore, there appears to be a typographical error as the company concluded that a Cox proportional hazards model showed that there was a statistically significant difference between treatments significant in favour of IsaPd despite the confidence interval for the HR crossing unity (HR= 0.642, 95% CI: 0.38, 1.082).

As before, the ERG is not confident that all of the models, for example the Generalised F distribution, are estimable from the sample data alone given the number of events in each treatment arm. Furthermore, it is unclear how the treatment effect is defined in some models (for example, the Generalised F distribution) or on what scale it is estimated.

As before, the company inappropriately projects a HR from a Cox proportional hazards model onto an acceleration failure model survival function (the lognormal) for IsaPd to generate the PanVd survival function. The magnitude of any inaccuracy associated with this is unknown, but it is unlikely to alter the conclusions of the company's economic analysis of IsaPd compared to PanVd.

Objective Response Rate (ORR)

In Section K.4.4 of the CS,[3] the company wrote that it did not consider a comparison of ORR on the basis that studies used different response definitions. Nevertheless, Section K.4.5.4 presents a MAIC between IsaPd and PanVd. No information is provided on the weights. Estimates of odds ratios and risk differences are provided according to unweighted and weighted data; these are virtually identical suggesting no adjustment for differences in study characteristics.

3.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

3.6 Conclusions of the clinical effectiveness section

3.6.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The clinical evidence relating to isatuximab with pomalidomide and dexamethasone for treating RRMM is based on the ICARIA-MM trial,[4, 11] a Phase III open-label RCT. The ERG is confident that no additional studies (published or unpublished) of isatuximab with pomalidomide and dexamethasone for treating RRMM are likely to have been missed.

3.6.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

The ERG is confident that the relevant population, intervention and comparators have been included in the CS. The primary outcome of the ICARIA-MM trial was PFS, assessed from the date of randomisation to the date of first documentation of progressive disease or the date of death from any cause, whichever came first, at the cut-off date (11th October 2018), which is a recommended outcome according to the EMA.[12] In the 4L population, the median PFS was greater in the IsaPd arm (13.31 months [95% CI: 7.425, not calculable]) than in the Pd arm (7.82 [95% CI: 4.468, 11.072]), and the stratified (by age) HR was 0.598 (95%: CI 0.348, 1.030), which the CS states represents a 40.2% risk reduction of disease progression or death in favour of IsaPd compared with Pd.[3] The EMA suggest that OS should demonstrate a trend towards superiority if PFS is used as a primary outcome.[12] Mortality events were reported in 21.2% and 39.7% of 4L patients in the IsaPd and Pd arms, respectively, with a median OS of 14.36 months (95%: CI 11.565, not calculable) in the Pd arm whilst the median OS had not been reached in the IsaPd arm (stratified HR 0.494 [95% CI 0.240, 1.015]), which indicates a trend for greater OS in the IsaPd arm. The OS data, however, were immature and final OS analyses are planned once 220 deaths have been observed. The effect of IsaPd on OS may have been impacted by an imbalance between the trial arms in the proportion of patients who received subsequent daratumumab. ORR and median TTP were higher in the IsaPd arm of the 4L population than the Pd arm. The median DOR was not calculable for both the IsaPd and Pd arms in the 4L population, and no clinically meaningful difference between treatment arms on EORTC QLQ-C30 scores and subscale scores, suggesting no QoL detriment of IsaPd in relation to treatment with Pd. In terms of AEs, IsaPd appears to be generally well tolerated.

3.6.3 Uncertainties surrounding the reliability of the clinical effectiveness

The first key uncertainty relates to the open-label nature of the trial, which may have introduced measurement bias, and may have altered patterns of oral medication use (e.g. for oral pomalidomide, the RDI of which was higher in the Pd arm than in the IsaPd arm). The impact of this element of study design is difficult to assess, however it is unlikely that this would have made no impact on the results.

The second key uncertainty relates to the post-hoc analysis and reporting of patients in the ICARIA-MM study at 4L of treatment. The 4L population is directly relevant to the proposed positioning of IsaPd within the treatment pathway, however the ERG has some reservations with this *post hoc* approach, as it was not a stratified group and does not have the protection of the randomisation when making comparisons between treatments.

A discrepancy between the arms in the use of subsequent daratumumab introduces uncertainty in the measurement of OS. Since subsequent daratumumab use (at 5L) is inconsistent with the current UK

clinical management pathway for RRMM, this may compromise the generalisability of the ICARIA-MM study results to the UK context.

The ERG notes that the MAIC used to compare IsaPd and PanVd will have inherent uncertainties as detailed in Section 3.4. This also represents a key uncertainty.

4 COST EFFECTIVENESS

This chapter presents a summary and critique of the company's health economic analyses of isatuximab with pomalidomide and dexamethasone for the treatment of adult patients with RRMM. Section 4.1 presents a critique of the company's review of existing health economic analyses. Section 4.2 summarises the methods and results of the company's model. Sections 4.3 and 4.4 present the critique of the model and additional exploratory analyses undertaken by the ERG, respectively. Section 4.5 presents a discussion and critique of the available economic evidence.

The three key components of the economic evidence presented in the CS are: (i) a systematic review of the relevant literature, (ii) a report of the company's *de novo* economic evaluation and (iii) a presentation of the incremental cost effectiveness ratio (ICER) in terms of cost per quality-adjusted life year (QALY) gained. The company also provided an electronic version of their economic model developed in Microsoft Excel®. Following the clarification process the company submitted a revised version of the model that included updated estimates of the cost-effectiveness of IsaPd. For brevity, this report will only refer to the model (and results) received after clarification, unless explicitly stated otherwise. Despite advice provided by NICE, the company maintained the use of estimated confidential PAS discounts for daratumumab, pomalidomide and panobinostat in its base case, although results were also presented with these estimated discounts removed. The ERG has only reported on the results without inclusion of the estimated PAS discounts; results with the PAS discounts for pomalidomide, panobinostat and lenalidomide included are contained in a confidential report.

4.1 Company's review of published cost-effectiveness studies

4.1.1 Summary and critique of the company's search strategy

The company performed a three-in-one systematic literature search to identify: (i) economic evaluations of isatuximab and its comparators for treatment of patients with RRMM (CS Appendix H, pages 139-152); (ii) HRQoL studies for patients with RRMM (CS Appendices H and I, pages 185-198), and; (iii) resource used data for patients with RRMM in England (CS Appendices H, I and J, pages 212-224).[3]

The following sources were searched from inception until June 2019: MEDLINE and Epub Ahead of Print, In Process and & Other Non-Indexed Citations and Daily [via Ovid], Embase [via Ovid], Health Technology Assessment database [via CRD], NHS Economic Evaluation Database [via CRD], the Cost Effectiveness Analysis Registry [Center for the Evaluation of Value and Risk in Health], and the ScHARR Health Utilities Database [University of Sheffield]. Several cancer conference proceedings websites (American Society of Clinical Oncology, European Society for Medical Oncology, European Haematology Association Congress, European Hematology Association, American Society of Hematology, European Society of Hematology) were searched covering the period from 2015 until

2019. The company carried out supplementary searches using the websites for several international HTA agencies (NICE, SMC, CADTH, ICER).

The company's searches are clearly and fully reported in Appendices H, I and J of the CS.[3] The ERG considers that they are comprehensive and would retrieve important citations relating to all eligible studies.

4.1.2 Summary of company's review findings

The company identified twenty studies that met the inclusion and exclusion criteria, of which 18 were cost-utility analyses. Four of these were company submissions to NICE: daratumumab monotherapy;[23] ixazomib with lenalidomide and dexamethasone;[24] panobinostat with bortezomib and dexamethasone[25]; and pomalidomide with low-dose dexamethasone,[26] which the company used to inform its submission. As none of the identified studies included isatuximab the company developed a *de novo* model for use in this appraisal.

4.2 Description of company's health economic analysis

4.2.1 Model scope

As part of its submission to NICE, the company submitted a fully executable health economic model programmed in Microsoft Excel®. A summary of the company's base case model is summarised in Table 5. The company's base case analysis assesses the incremental cost-effectiveness of IsaPd versus Pd in patients with relapsed or refractory multiple myeloma who have received 3 lines of prior therapies including lenalidomide and a proteasome inhibitor. Additional analyses were provided for patients who had received only two prior lines of treatment and for patients who had three or more lines of prior treatment.

Table 5: Summary of company's base case model

Population	Adults with relapsed or refractory multiple myeloma who have received 3 lines of prior therapies, including lenalidomide and a proteasome inhibitor (4th line of treatment)
Time horizon	15 years, assumed to represent a patient's lifetime
Intervention	Isatuximab (plus pomalidomide and dexamethasone) (IsaPd)
Comparator	Pomalidomide and dexamethasone (Pd)
Outcome	Incremental cost per QALY gained
Perspective	National Health Service (NHS) and Personal Social Services (PSS)
Discount rate	3.5% per annum for both health outcomes and costs
Price year	NHS Reference Costs (2017/2018); 2019 for drug costs

IsaPd - Isatuximab with pomalidomide and dexamethasone; NHS - National Health Service; Pd - Pomalidomide and dexamethasone; QALY - quality-adjusted life year; PSS - Personal Social Services

The company provide secondary cost-effectiveness analysis comparing IsaPd versus PanVd in Appendix K.4 of the CS,[3] "*in order to satisfy the requirements of the NICE scope*". The company claims

that PanVd "*appears to be reserved for later line (i.e. ≥5th line) mainly due to its associated toxicities*". As stated in Section 2.3.3 this position was not universally supported by the clinicians providing advice to the ERG.

The economic analysis was undertaken from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) over a 15-year (lifetime) horizon. Cost-effectiveness is expressed in terms of the incremental cost per QALY gained. Unit costs are valued at 2017/2018 prices, although the drug costs use 2019 prices.[3, 27] Health outcomes and costs are discounted at a rate of 3.5% per annum.

Population

The modelled population relates to adult patients with RRMM, who have received 3 lines of prior therapies, including lenalidomide and a proteasome inhibitor (4th line of treatment). This population is consistent with a subgroup of the ICARIA-MM study,[11] the final NICE scope[6] and the anticipated marketing authorisation for isatuximab. At model entry, patients are assumed to have a mean age of 65.9 years, a body surface area (BSA) of 1.8m^2 of, and 51.8% of patients are assumed to be male.[3] The company states (CS, page 96) that *"although the patients entering the model are younger than those expected to be treated in the UK, evidence from ICARIA demonstrates consistent outcomes across all pre-specified subgroups including age (<75 years versus >=75 years) and number of previous lines (2 or 3 versus >3)"*.[3] However, the ERG notes that similar relative outcomes, such as HRs, between subgroups does not necessarily translate into similar ICERs if there are differences in aspects such as underlying prognoses.

Clinical specialists consulted by the ERG agreed that the population of the study appears reasonably consistent with the population being treated in clinical practice in England, albeit with a smaller proportion of black patients than would be expected in the UK. Clinical advice stated that this racial discrepancy was unlikely to significantly affect applicability to patients with RRMM in the UK.

Intervention

The intervention evaluated in the submission is IsaPd. Within the model, isatuximab is assumed to be administered as an infusion at a dose of 10mg/kg on days 1, 8, 15, and 22 for the first four weeks; and on days 1 and 15 subsequently of four-week periods. Dexamethasone is assumed to be administered orally or as an IV at a dose of 20mg or 40mg on days 1, 8, 15 and 22 of every four weeks. Pomalidomide is assumed to be administered orally at a dose of 4mg on days 1 to 21 of every four weeks. The model also considers medication used prior to isatuximab infusion with the objective of reducing the risk and severity of infusion reactions. Such interventions include: acetaminophen 650mg to 1000mg orally (paracetamol 1000mg); H2 antagonists (ranitidine 50mg IV); and cetirizine 50mg as an IV (as an equivalent to diphenhydramine 25mg to 50mg).[3]

Comparators

The comparator evaluated within the company's base case analysis is Pd, a combination of pomalidomide and dexamethasone, where the constituent parts are assumed to be administered according to the same schedule as the intervention. The model also includes the costs of acetylsalicylic acid, at a dose of 325mg given orally for 21 days of every four weeks.

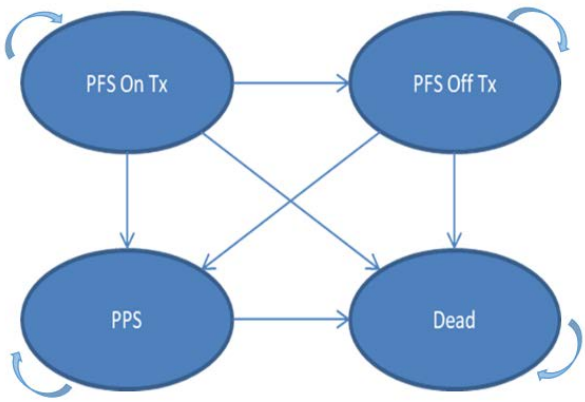
PanVd, the comparator presented in a secondary cost-effectiveness analysis (CS, Appendix K.3),[3] is a combination of panobinostat (20mg/day orally, for 6 days every three weeks); bortezomib (1.3mg/m^2 via injections, for 4 days in every three weeks for the first 24 weeks and then for 2 days every 3 weeks for 24 weeks); and dexamethasone (20mg/day orally, for 4 days every three weeks for the first 24 weeks and for 2 days every three weeks for 24 weeks). The dosing scheme for PanVd is based on the Summary of Product Characteristics (SmPC) for panobinostat from the EMA.[28]

Drug acquisition costs for IsaPd, Pd and PanVd over the patient's lifetime are based on the probability of patients remaining on each treatment based on time to treatment discontinuation (TTD) functions.

4.2.2 Model structure and logic

The general structure of the company's economic model is described in CS (pages 96-98),[3] as a partitioned survival model approach, based on four health states: (i) event-free on treatment; (ii) event-free off treatment; (iii) post-event, and (iv) death (see Figure 4). It is possible to remain in the same health state between cycles.

Figure 4: Company's model structure (adapted from CS, Figure 20)



The ERG notes that the original approach adopted by the company was chosen in preference to a more conventional three-state model in order to allow for the use of different utility values for patients conditional on whether people were on or off treatment. During the clarification process,[7] the company

adopted an alternative approach to calculating the health state QALYs, where utility in the PFS and PD health states was assumed to be independent of whether or not the patient is on treatment. However, the structure that allows for different utilities to be included remains. As a result, the revised model can be considered to be operating as though it were a partitioned survival model with three health states: (i) progression-free and alive; (ii) post-progression and alive, and (iii) dead. For simplicity, the ERG reports parameters as though the model was constructed as a three-state partition survival model. No assumptions of patients being cured from the disease were explicitly introduced by the company in its submission and model. The ERG comments that the model was relatively cumbersome and had a file size approaching 40 Megabytes, which is excessive for a partitioned survival model.

Within the company's model, patients enter the model in the progression-free and alive state and receive 4L treatment with either IsaPd or Pd. PFS, TTD and OS are modelled using treatment group-specific parametric distributions fitted to time-to-event data for patients from the 4L subgroup in ICARIA-MM RCT.[11] A mortality constraint is applied to ensure that the probability of survival for the modelled population does not exceed that of the general population of the UK.[27]

The probability of being in each model state at time *t* is estimated for each health state as follows:

- PFS: This is calculated using the PFS survival function (constrained by the OS function and general population mortality) at time *t*.
- PPS: This is calculated as the difference between the cumulative survival probabilities at time *t* for OS and PFS;
- death: This uses the OS survival function (constrained by general population mortality) at time *t*.

Time on 4L treatment was estimated from TTD survival function.

HRQoL is assumed to be determined by the patient's health state (progression-free or post-progression) and the type of treatment received (IsaPd or Pd). Health utilities used in the model are based on the results of a generalised estimating equation (GEE) model fitted to derived EuroQoL Group self-report questionnaire with 5 dimensions (3 level) (EQ-5D-3L) data. EQ-5D-3L data were derived from the EQ-5D-5L data collected in ICARIA-MM, using the mapping algorithm reported by Van Hout *et al.*[29] EQ-5D-3L estimates were adjusted for patient-aging using the relationship reported by Ara and Brazier.[30] The company includes a QALY decrement to capture the decline in HRQoL during the terminal phase of the disease, which was also derived from the trial data. The model does not explicitly include any QALY loss associated with Grade 3/4 AEs for IsaPd or Pd. The company states that the effects of AEs on HRQoL would already have been captured in the EQ-5D data collected from patients event-free and on treatment in ICARIA-MM (CS, page 129).[3]

The model includes costs associated with: (i) drug acquisition and administration; (ii) disease management ('follow-up and monitoring', and 'concomitant treatments'); (iii) treatments following disease relapse/progression; (iv) management of AEs; and (v) end of life care. Drug acquisition and administration costs are modelled using the TTD survival function, the planned treatment schedule, RDI and unit costs. Disease management costs include medical visits, blood tests and biochemistry, and the costs of concomitant treatments (granulocyte colony stimulating factor (GCSF), blood and platelet transfusions); these costs are presented in Section 4.2.4. Whilst the costs of the visits and tests are applied in all cycles to the number of patients in each health state, the costs of concomitant treatments are applied as once-only costs in the first model cycle to all patients. Costs related to the management of AEs are also applied as once-only costs in the first model cycle; end of life care costs are applied as a fixed cost in the cycle in which the patient died, while costs of treatments in 5L are added as a fixed sum in the cycle at which a patient discontinues.

The incremental health gains, costs and cost-effectiveness of IsaPd versus Pd are modelled in a pairwise fashion based on the difference in costs divided by the difference in QALYs for IsaPd and Pd, over a time horizon of 15 years using 1-week cycles. Half-cycle correction is not applied to account for the timing of events, due to the short cycle length. Secondary analyses are presented in the CS (Appendix K.3 and K.4)[3] for comparisons against IsaPd versus PanVd for 4L, and for IsaPd versus Pd for 3L, 3L+ and 4L+. This report focusses predominantly on the company's base case analysis, which is the comparison of IsaPd compared with Pd for patients with RRMM receiving 4L treatment.

4.2.3 Key assumptions employed in the company's model

The company's model employs the following key assumptions in its base case:

- PAS discounts for daratumumab, pomalidomide and panobinostat were applied despite prevailing NICE guidance; results without these discounts were also provided;
- An exponential distribution was used for modelling OS, and for TTD. A jointly-fitted lognormal model with a treatment effect covariate was used for PFS;
- Acquisition costs of the intervention and comparators (drug costs) are modelled using the TTD survival functions;
- HRQoL is assumed to be conditional on two factors: (i) whether a patient is in PFS or PPS (although in the revised model these were set to the same value), and (ii) which 4L treatment was received, based on estimates derived from the GEE model fitted to the data collected in ICARIA-MM;
- A utility decrement of 0.225 (estimated from the GEE model) is applied for three months prior to death, irrespective of the treatment received, to reflect a deterioration on the quality of life

in this period. The 12-week period was based on published literature and review of the study data;[11, 31, 32]

- The proportion of patients receiving 5L treatment following IsaPd or Pd were based on data from ICARIA-MM;[11] however, the mean duration of each therapy was based on external data;[33]
- The frequency of follow-up and monitoring interventions (physician visits, complete blood tests and biochemistry) were assumed independent of treatment and progression status, based on clinical opinion provided to the company;
- Only the top 10 most frequently prescribed medications were included in the costs of 5L treatment;
- The cost of terminal care was assumed to be the same irrespective of the treatment received (£894.15), based on a previous submission to NICE for pomalidomide;[34]
- The model considers only AEs that were reported in ≥5% of patients in any of the treatment arms of ICARIA-MM[11] and that were judged to be Grade 3 or higher in severity. The probabilities were taken from the observed data of 4L patients in ICARIA-MM[11] with the costs sourced from NHS Reference Costs 2017/18.[35] Disutilities were assumed to be already captured on the mean utility values generated from ICARIA-MM data.

The company's model employs the following additional key assumptions in its comparison of IsaPd and PanVd:

- The HRs obtained from the MAIC were applied to the survival functions for OS and PFS associated with IsaPd in the company base case; the HR obtained for PFS was assumed to be applicable to the survival function for TTD;
- The health state utilities and terminal decrement for patients on IsaPd were assumed to be applicable to PanVd;
- The probabilities of patients on PanVd having AEs, their duration, disutilities, and associated costs were estimated based on previous daratumumab NICE STA (TA510),[36] lenalidomide NICE STA,[37, 38] and other published sources.[39-45] The probabilities of having AEs were assumed to be applicable to patients on 4th line of treatment for RRMM, even if the original data were not specific to this group of patients.[3]
- The proportion of patients receiving each 5L therapy following IsaPd were assumed to be generalisable to PanVd.

4.2.4 Evidence used to inform the company's model parameters

The sources of evidence used to inform company's model parameters are summarised in Table 6. These are discussed in detail in the subsequent sections.

Table 6: Summary of evidence used to inform the company's base case analysis and comparison of IsaPd and PanVd

Parameter group	Source
Base case analysis – comparison of IsaPd and Pd for 4L	
Patient characteristics (age, BSA, weight, proportion of females)	The 4L subgroup in ICARIA-MM[4]
TTD – IsaPd and Pd	An exponential model fitted to observed TTD data for 4L subgroup in ICARIA-MM[11]
PFS – IsaPd and Pd	A jointly-fitted lognormal model with a treatment effect covariate fitted to observed PFS data from each treatment group (4L subgroup) in ICARIA-MM[11]
OS – IsaPd and Pd	An exponential model fitted to observed OS data from each treatment group (4L subgroup) in ICARIA-MM[11]
Mortality – general population constraint	Derived from interim life tables for England 2016-2018[27]
HRQoL for health states – IsaPd and Pd	GEE model fitted to EQ-5D-5L data collected from 4L subgroup on IsaPd or Pd in ICARIA-MM[11] (mapped to EQ-5D-3L using van Hout *et al*[11, 29])
End of life HRQoL decrement – IsaPd and Pd	GEE model fitted to EQ-5D-5L data collected from 4L subgroup on IsaPd or Pd in ICARIA-MM (mapped to EQ-5D-3L using van Hout *et al*)[11, 29]
Duration of the end of life HRQoL decrement	Based on previous literature and review of the data from ICARIA-MM[4, 31, 32]
HRQoL age-adjustment	Age- and gender-matched general population utilities based on published UK population norms from Ara and Brazier[30]
The proportion of patients experiencing AEs - IsaPd and Pd	Based on data from 4L subgroup on IsaPd or Pd in ICARIA-MM[11]
AE disutility – IsaPd and Pd	Not explicitly included. The company assumed that the utility values for PFS in ICARIA-MM[11] captured the effects of AEs on HRQoL.[3]
Drug acquisition costs – IsaPd and Pd	Unit costs from Electronic Market Information Tool (eMIT)[46] and British National Formulary (BNF),[47] estimates of BSA, weight and RDI obtained from ICARIA-MM[11]
Drug administration costs – IsaPd and Pd	Unit costs taken from NHS Reference Costs 2017/18[35]
Disease management costs (follow-up and monitoring) – IsaPd and Pd	Daratumumab NICE STA (TA510),[36] NHS Reference Costs 2017/18.[35] Clinical opinion was used for the frequency of monitoring.
Disease management costs (concurrent treatment) – IsaPd and Pd	Daratumumab NICE STA (TA510)[36] and pomalidomide submission to NICE (TA427);[34] unit costs taken from NHS Reference Costs 2017/18[35]
Post-progression treatment costs (subsequent therapy) – IsaPd and Pd	Unit costs from eMIT[46] and BNF[47]
Probability of receiving each of the subsequent therapy considered– IsaPd and Pd	Based on data for the ten most frequently received treatments in ICARIA-MM[11]
Mean duration of subsequent therapy – IsaPd and Pd	Values from external data.[33] PanVd submission to NICE,[48] and NHS regimen information sheets for etoposide and bendamustine.[49, 50]
Costs associated with AEs – IsaPd and Pd	AE frequencies based on ICARIA-MM;[11] unit costs taken from NHS Reference Costs 2017/18[35]
End of life care costs – IsaPd and Pd	Pomalidomide submission to NICE (TA427),[34] updated to 2017/2018 costs[35]

Parameter group	Source
Additional analysis – evidence used to inform PanVd in the comparison of IsaPd and PanVd for 4L	
OS – PanVd	An estimate of the HR for OS for PanVd vs. IsaPd from the MAIC-adjusted unanchored comparison between ICARIA-MM[11] (IsaPd) and PANORAMA-2[9] (PanVd), applied to the OS function for IsaPd
PFS – PanVd	An estimate of the HR for PFS for PanVd vs. IsaPd from the MAIC-adjusted unanchored comparison between ICARIA-MM[11] (IsaPd) and PANORAMA-2[9] (PanVd) was applied to the PFS function for IsaPd
TTD – PanVd	Estimates of the HR for PFS for PanVd vs. IsaPd from the MAIC-adjusted unanchored comparison were applied to the TTD function for IsaPd
HRQoL for health states – PanVd	The company assumed the same values as for IsaPd
End of life HRQoL decrement – PanVd	The company assumed the same values as for IsaPd and Pd
Probabilities of patients having AEs - PanVd	Estimates of the probabilities for PanVd are based on data from the daratumumab NICE STA (TA510);[36] values not specific to 4th line of treatment; which are adjusted by subtracting from it the probability of having each AE from the IsaPd treatment group (based on ICARIA-MM)[7, 11]
AE disutility – PanVd	AE estimates of the disutilities and their duration based on daratumumab NICE STA (TA510),[36] lenalidomide NICE STA,[37, 38] and other published sources[39-45]
Drug acquisition costs – PanVd	Unit costs from eMIT[46] and BNF;[47] regimen based on SmPC for panobinostat;[28] RDI based on PANORAMA-2 data[9]
Drug administration costs – PanVd	Unit costs taken from NHS Reference Costs 2017/18.[35]
Disease management costs (follow-up and monitoring) – PanVd	The frequency of physician visits and blood tests was assumed to be the same as for IsaPd and Pd
Disease management costs (concurrent treatment) – PanVd	The average number of interventions from daratumumab NICE STA (TA510);[36] unit costs taken from NHS Reference Costs 2017/18[35]
Post-progression treatment costs (subsequent therapy) – PanVd	Subsequent treatment after progression was assumed to be the same as for IsaPd and Pd
Probability of receiving each of the subsequent therapy considered – PanVd	The company assumed the same values as for IsaPd
Mean duration of subsequent therapy – PanVd	The company assumed the same values as for IsaPd and Pd
Costs associated with AEs – PanVd	Estimated costs for each AE from Daratumumab NICE STA (TA510)[36] and NHS Reference Costs 2017/18.[35]
End of life care costs – PanVd	The company assumed the same costs per patient as for IsaPd and Pd

AE - adverse event; BSA - body surface area; PFS - progression-free survival; EQ-5D - EuroQoL 5-dimensions; GEE - generalised estimating equation; HRQoL - health-related quality of life; IsaPd – isatuximab in combination with pomalidomide and dexamethasone; eMIT - Electronic Market Information Tool; OS - overall survival; PanVd – panobinostat, with bortezomib and dexamethasone; Pd – pomalidomide and dexamethasone; RDI - relative dose intensity; STA – single technology appraisal; TA – technology appraisal.

4.2.4.1 *Patient characteristics at model entry*

The model assumes that patients enter the model aged 65.9 years and approximately 51.8% of the modelled cohort is assumed to be male. Patients are assumed to have a mean body surface area (BSA)

of 1.8m^2 and to weigh 73.14kg. These characteristics reflect the population of patients who have received three prior lines of treatment (4L) in the ICARIA-MM trial.[11]

4.2.4.2 *Description and critique of the company's survival analyses*

For each of the outcomes used in the economic model (PFS, OS and TTD), six standard parametric models were fitted (exponential, Weibull, log-logistic, lognormal, generalised gamma and generalised F distributions). Survival functions were also estimated using restricted cubic splines (RCS).

The company's preferred base case model was based on the treatment effect diagnostics and test of linearity of Schoenfeld residuals for the proportional hazards assumption, statistical goodness-of-fit, visual comparison with empirical Kapan-Meier survival functions and the clinical plausibility of the projected survival functions.

The company fitted the same models to each arm of the ICARIA-MM study,[4] partly to allow estimation of a single treatment effect. However, this approach assumes that the treatment effect is constant over time on some appropriate scale (i.e. proportional hazards, acceleration failure or proportional odds). While this approach is a convenient modelling assumption for estimating a treatment effect, there is no stated clinical reason why the treatment effect should be constant over time. Making this assumption when the treatment effect is not constant will generate biased estimates of population mean survival. To relax this assumption, the company also fitted separate but identical models to each treatment arm.

Section B.3.3 of the CS[3] states that "*the RCS distributions have six parameters, not including the knots*". However, a proportional hazards restricted cubic spline model with a single covariate representing a constant treatment effect and including a single knot is:

$$\ln[H(t; z_1)] = \gamma_0 + \gamma_{10}x + \gamma_{20}v_1(x) + \beta_1 z_1$$

Thus, a proportional hazards model including one knot has four parameters, while a non-proportional hazards model including a single knot would have six parameters. Hence, it is not clear to what parameters the company is referring.

The results of the MAIC may appear to lack face validity as PanVd is estimated to have a shorter time to progression than Pd, [PanVd HR compared with IsaPd (0.369 (0.259 – 0.526)) whereas Pd compared with IsaPd (0.598 (0.348 – 1.030))] but is estimated to have a shorter survival [PanVd HR compared with IsaPd (0.642 (0.380 – 1.082)) whereas Pd compared with IsaPd (0.494 (0.240 – 1.015))]. Typically, PFS is correlated with OS as death is counted as an event in both metrics.

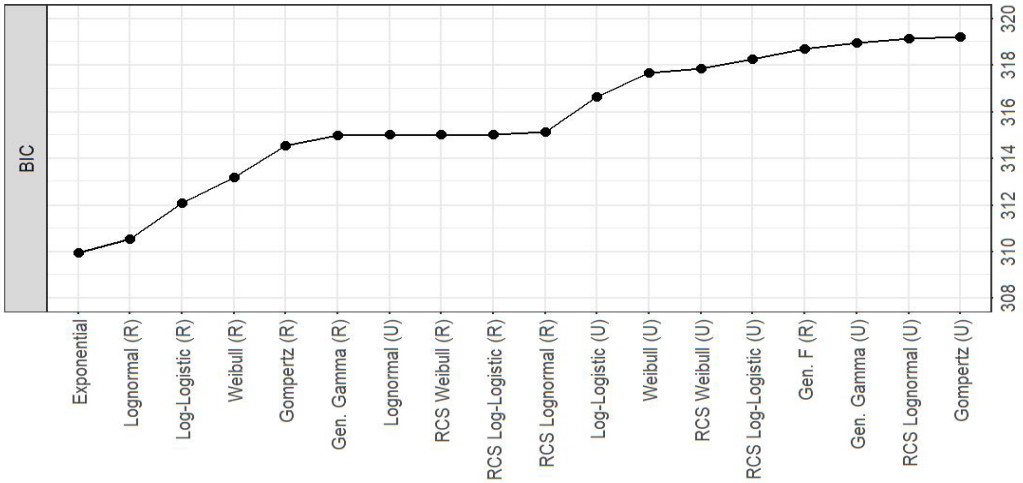
4.2.4.2.1 Description and critique of the company's model fitting to OS data

Section B.3.3 of the CS refers to restricted cubic spline Weibull, lognormal and log-logistic models. However, it is not clear to the ERG what is meant by this. Weibull, lognormal and log-logistic models can be parameterised using a restricted cubic spline approach depending on the link function used and by including no additional knots. These analyses should give the same results as for standard parameterisations of these models.

The company assesses the clinical plausibility of projected survival functions against available external evidence (e.g. the MM-003 study[51]) and through a series of interviews with three NHS consultant haematologists. The ERG notes that assessing the consistency of extrapolations against data from other studies is difficult without taking into account differences in patient characteristics. Furthermore, the ERG believes that asking clinical experts to indicate which, in their opinion, is the most plausible of a set of survival functions is unlikely to be very informative for the following reasons: first, it implies that a clinical expert is able to express their opinion about the true proportion of patients surviving at each time without any uncertainty; second it ignores uncertainty associated with the parameters of each model, and the consequent uncertainty associated with the survival functions; and third survival functions derived from distributions with very different underlying hazards may look similar to clinical experts. In practice, questions regarding beliefs about the proportion of patients event-free at different follow up times should be asked using a formal elicitation of experts' beliefs before seeing data from a study, although the ERG acknowledges that this was unlikely to be possible in this case. However, based on the information presented in the CS, the ERG considers an exponential distribution, as selected by the company, to provide a reasonable representation of the OS data. The BIC data for the fits to OS provided within the CS are reproduced in Figure 5. The company used (R) to denote jointly-fitted models with a treatment effect covariate models and (U) models fitted independently to each arm.

The ERG notes that other functions (jointly-fitted lognormal, jointly-fitted log-logistic and jointly-fitted Weibull models in particular) provide similar a fit to the known OS data, but these were not independently explored within the scenario analyses undertaken in the CS, despite the fact that two of three NHS consultant haematologists preferred the extrapolation from the Weibull model.[3] The company justified the decision to not use the Weibull survival function as "*almost all patients are dead by 5 years on Pd arm and by 10 years on IsaPd. There are no patients alive after 10 years, which is inconsistent with the feedback and published evidence regarding long term survival for a small proportion of patients with RRMM*". The company states that, by contrast, the exponential survival function predicts approximately 10% alive at 10 years, and almost no patients alive at 15 years. Clinical advice to the ERG suggests that there would be practically no patients alive at 10 years given present treatment options.

Figure 5: Bayesian Information Criteria fit to OS data for the 4L population of ICARIA-MM (reproduced from Figure 22 of the CS)



The plot of the six best-fitting parametric models to the OS KM data are shown in Figures 27 and 28 of the CS.[3] However as they are not shown on a single graph the ERG has provided the fits to the IsaPd OS KM data in Figure 6 and the fits to the Pd OS KM in Figure 7. The models used in the company base case are shown in Figure 8.

Figure 6: Selected model fits to the KM OS data for IsaPd

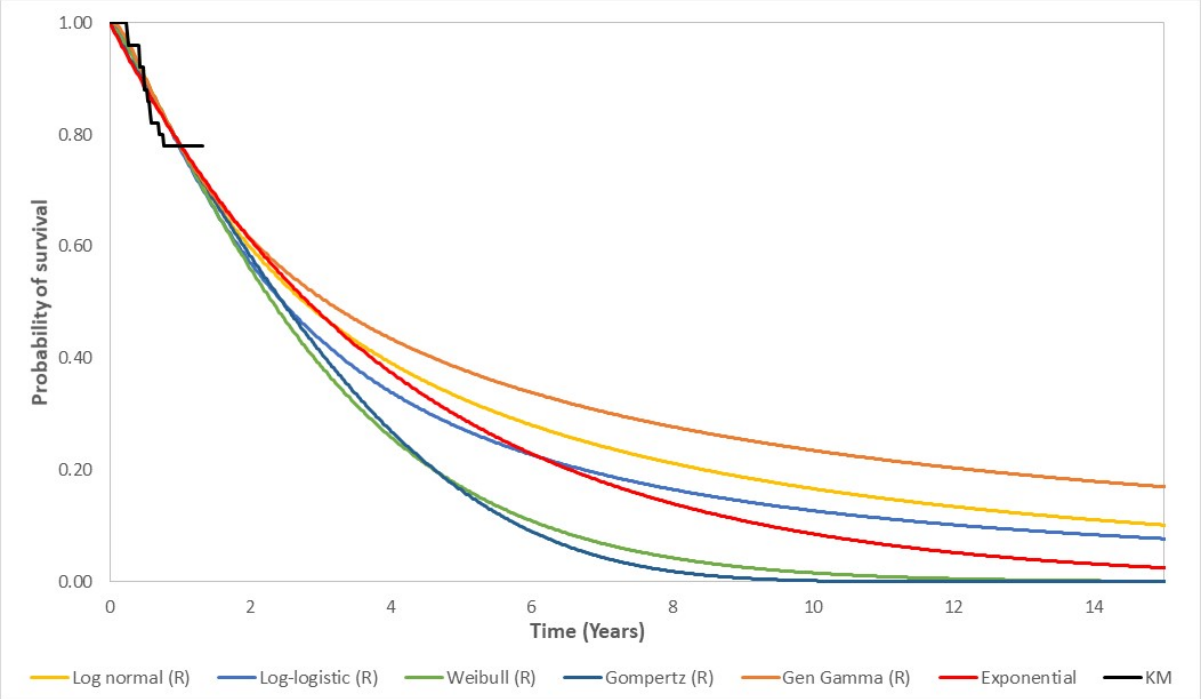


Figure 7: Selected model fits to the KM OS data for Pd

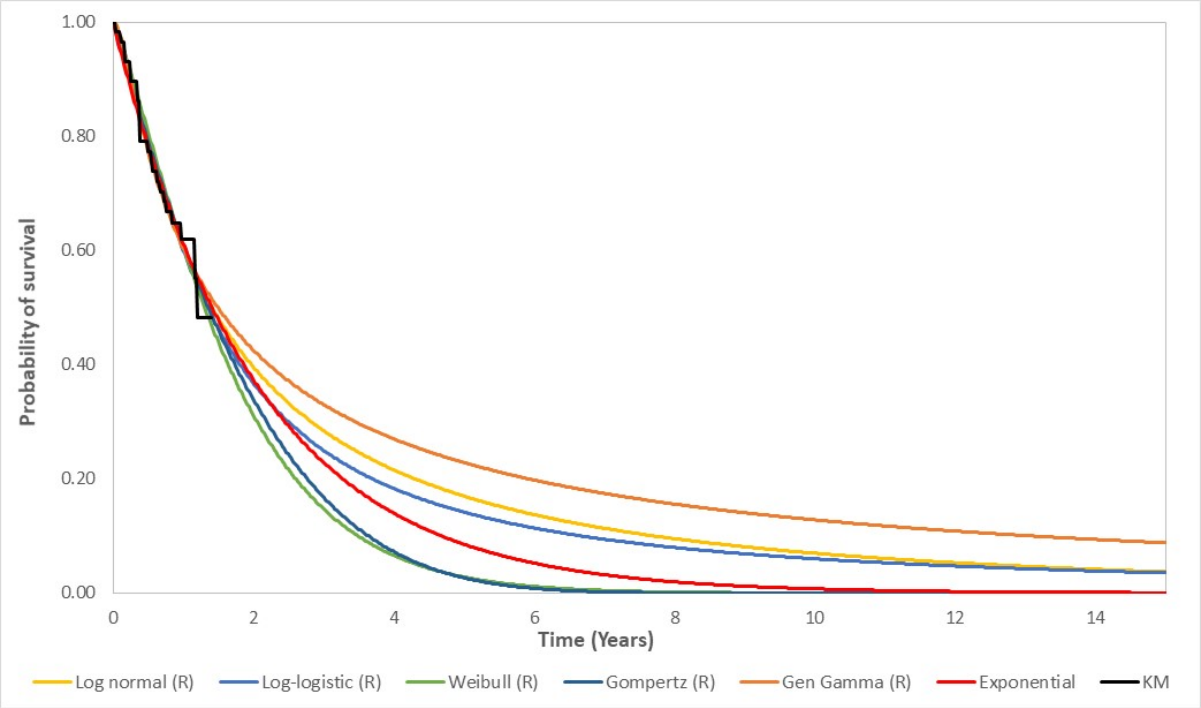
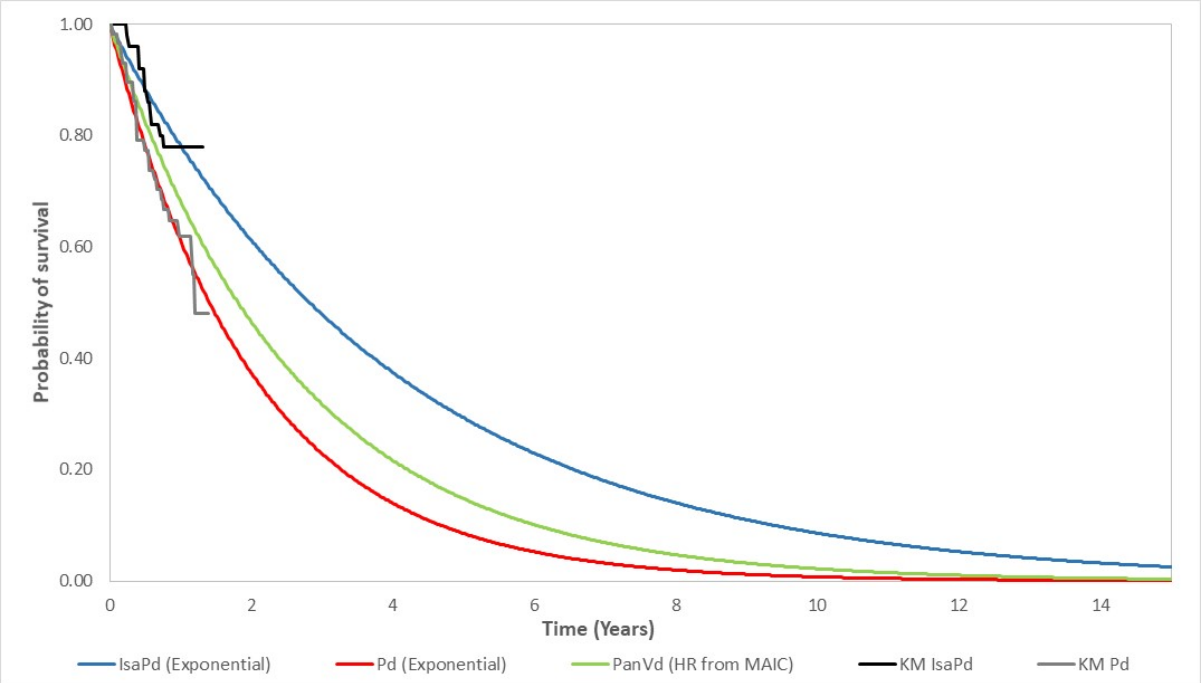


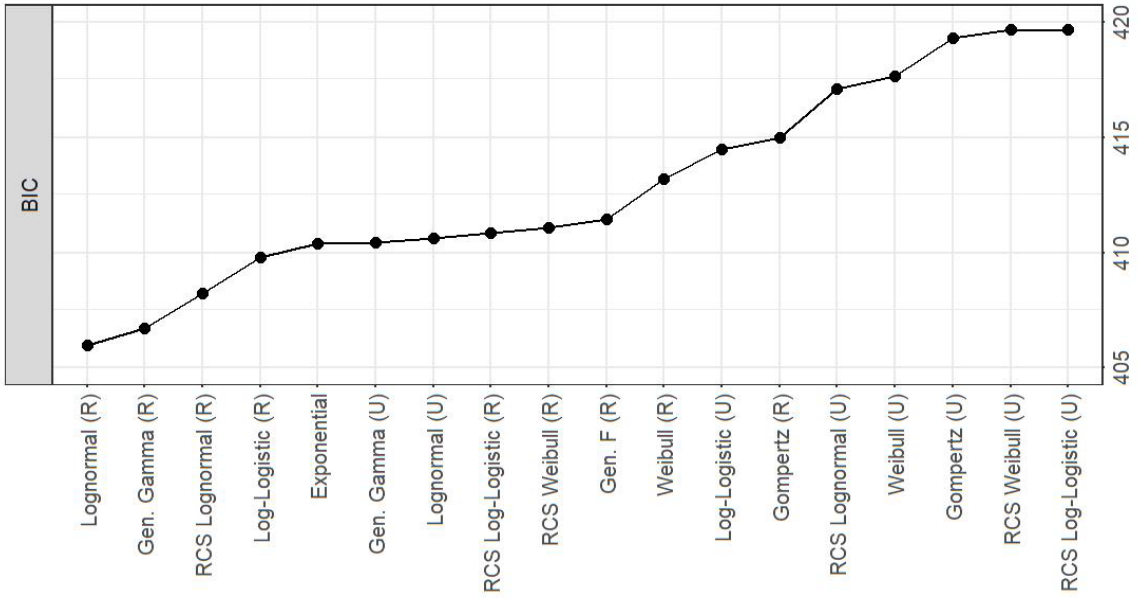
Figure 8: The models used for OS in the company's base case



4.2.4.2.2 Description and critique of the company's model fitting to PFS data

The BIC data for the fits to PFS provided within the CS[3] are reproduced in Figure 9. The ERG notes that there is a difference of approximately 5 in BIC with respect to the jointly-fitted lognormal distributions and independently fitted lognormal distributions.

Figure 9: Bayesian Information Criteria fit to PFS data for the 4L population of ICARIA-MM (reproduced from Figure 26 of the CS)



Whilst the ERG typically prefers independently-fitted models, as each treatment arm should represent the data better, it is noted that the difference in BIC reflects the fact that separate models are penalised more than a model allowing for an acceleration factor because of the use of an additional parameter. The ERG considers the jointly-fitted lognormal model with a treatment effect covariate to provide a reasonable representation of the PFS data. Alternative models for the PFS data that were preferred by clinical experts (the RCS jointly-fitted Weibull, the jointly-fitted Weibull, the exponential and the jointly-fitted Gompertz) were considered by the company in sensitivity analyses. The plot of the six best-fitting parametric models to the PFS KM data are shown in Figures 31 and 32 of the CS.[3] However, as these are not on a single graph the ERG has provided the fits to the IsaPd PFS KM data in Figure 10 and the fits to the Pd PFS KM in Figure 11. The models used in the company base case are shown in Figure 12.

Figure 10: Selected model fits to the KM PFS data for IsaPd

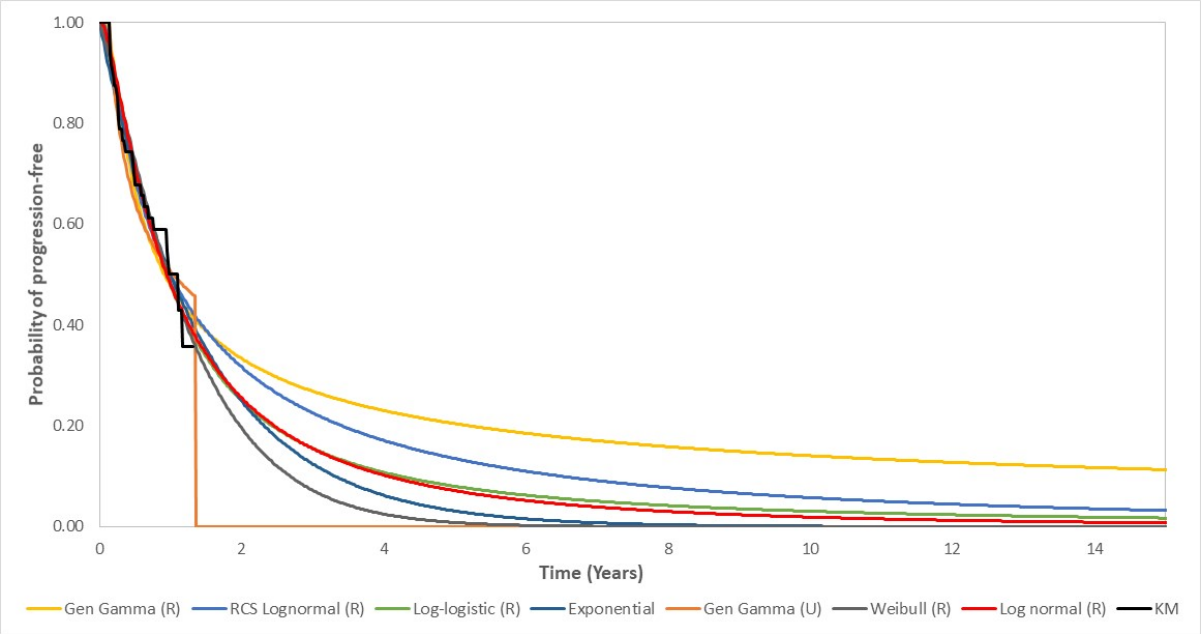


Figure 11: Selected model fits to the KM PFS data for Pd

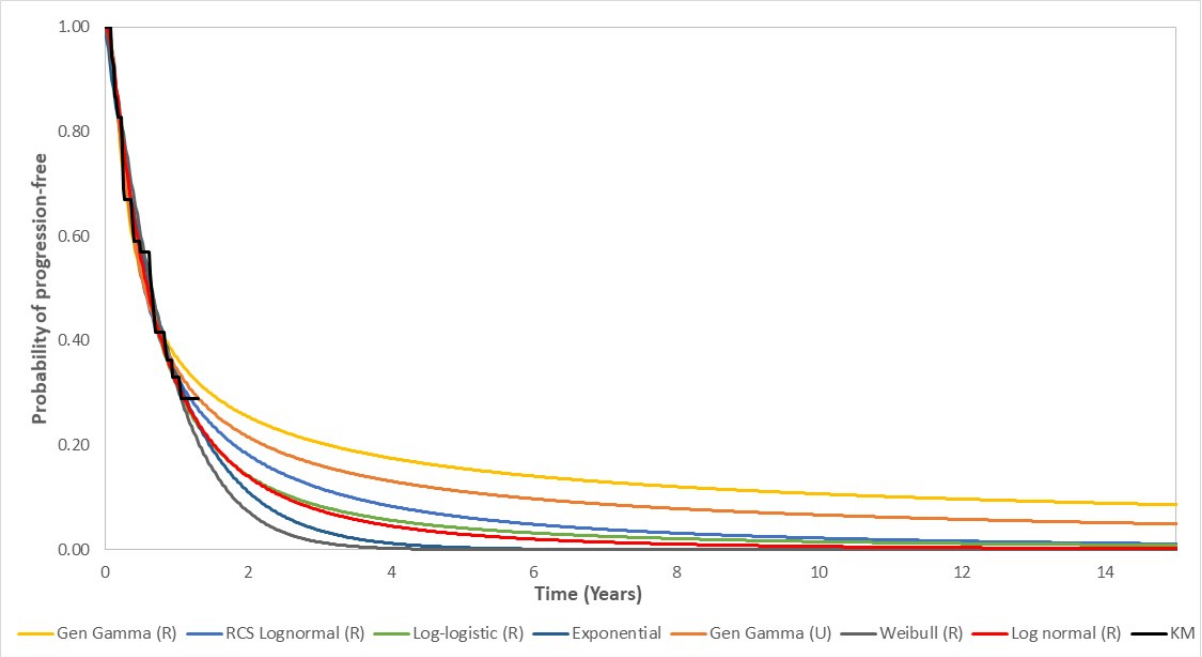
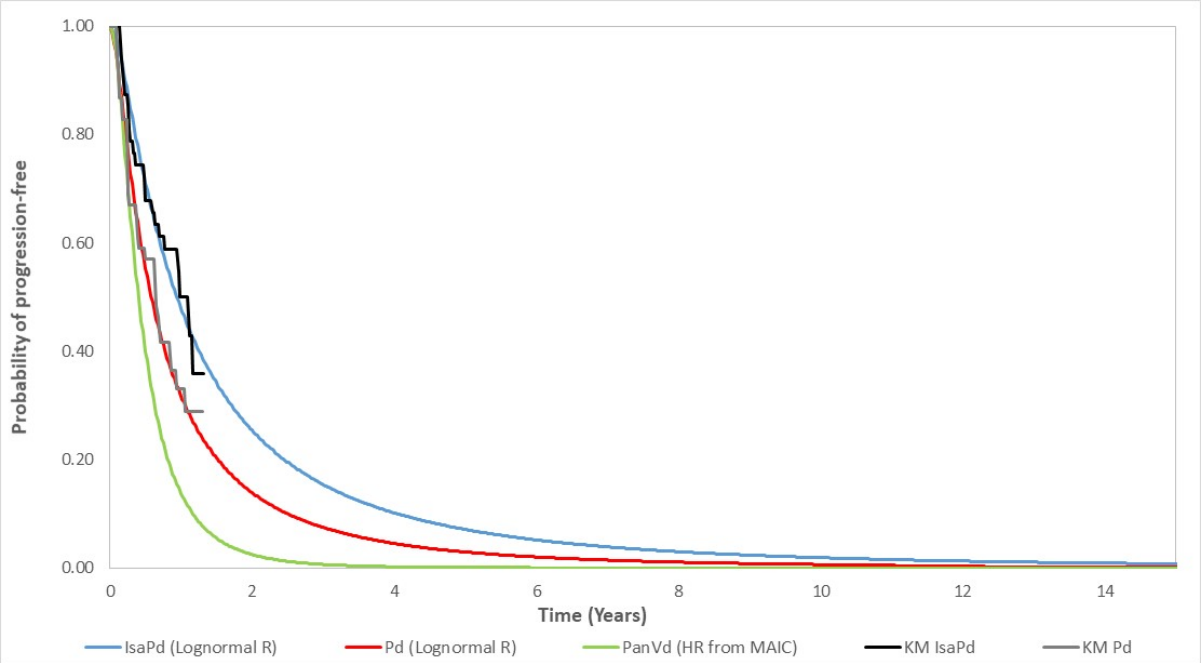


Figure 12: The models used for PFS in the company's base case



4.2.4.2.3 Description and critique of the company's model fitting to TTD data

The BIC data for the fits to TTD provided within the CS[3] are reproduced in Figure 13. It is seen that the exponential model has the lowest BIC value, which is nearly 5 lower than the remaining models. The plot of the six best-fitting parametric models to the TTD KM data are shown in Figures 35 and 36 of the CS.[3] However, as these are not on a single graph the ERG has provided the fits to the IsaPd TTD KM data in Figure 14 and the fits to the Pd TTD KM data in Figure 15. The models used in the company base case are shown in Figure 16.

The ERG believes that the exponential distribution, as selected by the company, appears to provide a good fit to the data but notes that the company did not report the results of scenario analyses using alternative functions.

Figure 13: Bayesian Information Criteria fit to TTD data for the 4L population of ICARIA-MM (reproduced from Figure 34 of the CS)

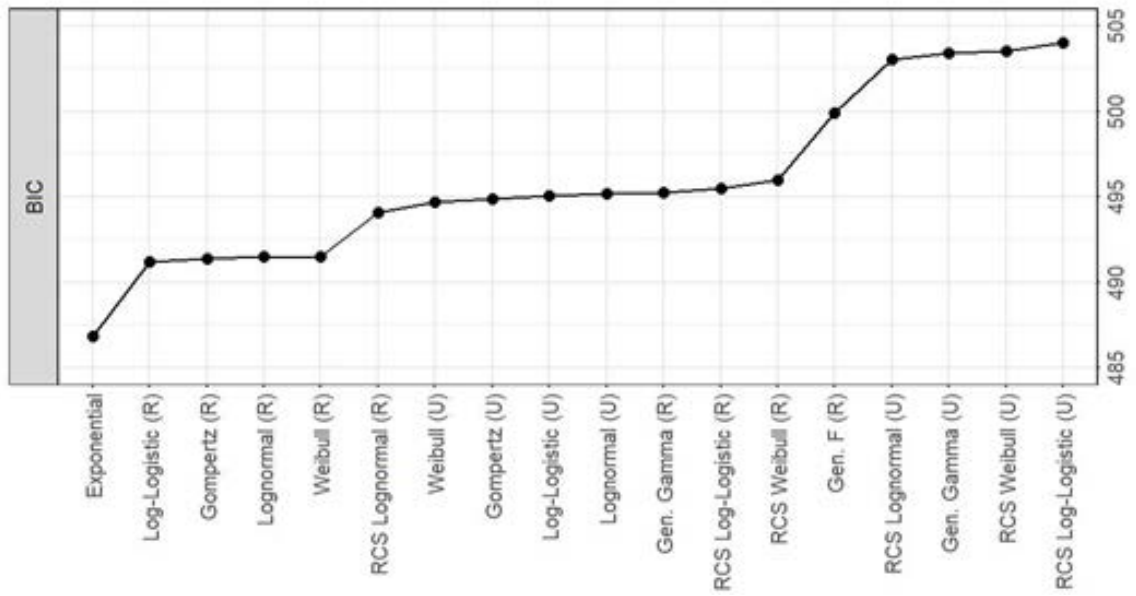


Figure 14: Selected model fits to the TTD PFS data for IsaPd (redacted – commercial in confidence)

[redacted]

Figure 15: Selected model fits to the TTD PFS data for Pd (redacted – commercial in confidence)

Figure 16: The models used for TTD in the company's base case (redacted – commercial in confidence)

Summary plots for the chosen fit to OS, PFS, PFS on treatment and TTD were provided in Figures 37 to 40 of the CS. The ERG is cautious regarding whether these plots are correct, as in the clarification process (question B6)[7] it was acknowledged that Figure 37 was incorrect and the ERG identified later that the projections of TTD using an exponential function appear different between Figures 35 and 39, with the ERG suspecting Figure 39 is erroneous. During the fact check process the company confirmed that Figures 37 to 40 of the CS were incorrect.

The ERG comments that when estimating parameters in time-to-event models using frequentist methods, the analysis generates a variance-covariance matrix. Although these estimates are approximations, they can be used to sample parameter estimates in time-to-event models from an approximate multivariate normal distribution.

4.2.4.3 HRQoL

Health state utility values

HRQoL data used in the company's model is based on data collected in ICARIA-MM[11] using the EQ-5D-5L questionnaire. Within the trial, the questionnaire was administered at day 1 of the first treatment course, and all subsequent cycles and at the 30-day end of treatment (EOT) visit and during the post-treatment follow-up period (60±5 days after last treatment administration).[11]

The company fitted a GEE model to the available data, using baseline utility value, treatment group, health state, and proximity to death as covariates whilst accounting for repeated measures in the same patient. Utility values were estimated for PFS and PPS health states, and also included a terminal decrement associated with the deterioration in the health of patients in the period ahead of death. The company has mapped the EQ-5D-5L data to the EQ-5D-3L using the algorithm reported by Van Hout *et al.*[29] and UK tariffs were applied to the 3L scores.[52]

The characteristics of the utility data and the estimates applied in the company's model are summarised in Table 7.[7] Utilities for the event-free state are assumed to be dependent on treatment group, whilst utilities for the post-progression state are assumed to be independent of previous treatment. These utilities values used in the model are applied in all cycles of the model.

Table 7: Mapped EQ-5D-3L estimates used in company's model (adapted from the company's model)

Health state	Mean utility†	
	IsaPd	Pd
Progression-free	0.719	0.717
Post-progression	0.611	0.611
End-of life (terminal) decrement	0.225	0.225

† Underlying utility values for PanVd were assumed equal to IsaPd. However, 0.035 QALYs were deducted in the first cycle to account for differing AE profiles.

The model applies age-adjustment to the health state utilities based on UK general population norms reported by Ara and Brazier.[30] Utilities for patients being treated with PanVd are assumed to be the same as for IsaPd patients.[7]

QALY losses due to AEs

A summary of the estimates for QALY losses related to AEs applied in the company's model is displayed in Table 8. The model does not include any decrements in QALYs associated with Grade 3 or higher AEs for IsaPd or Pd. The company states that the effects of AEs on HRQoL would already have been captured in the EQ-5D data collected from patients event-free and on treatment in ICARIA-MM (CS, page 129).[3] In response to clarification question B10 which asked whether it was possible that administering the EQ-5D prior to the dose of isatuximab would potentially overestimate utility, the company responded that "*it is typical to collect this data at the start of treatment cycle. In ICARIA-MM trial, EQ-5D were administered on day 1 of each cycle (i.e. every 2 weeks) therefore it is reasonable to assume that serious adverse reactions are likely to be captured in the subsequent EQ-5D questionnaire completed by the patient.*" The ERG believes that this is reasonable.

For patients in the PanVd group, the frequency of each AE considered was obtained from data for PanVd in the PANORAMA-2 study (reported in the company submission to NICE for daratumumab).[36] The company notes, however, that these values were not specific to patients who had 3 prior lines of treatment (CS, Appendix K.4, page 321).[3] The company calculates the difference between the IsaPd rates and those for PanVd to estimate the net change in utility from AEs.

Table 8: Frequency, associated utility decrements, mean duration and total disutilities associated with Grade ≥3 AEs (adapted from the company's model)

Adverse event	Frequency of AEs			Utility decrements	Mean duration (days)ǂ	Total disutilities		
	IsaPd	Pd	PanVd*			IsaPd§	Pd§	PanVd
Abdominal distension	0.0%	0.0%	7.3%	0.05	28	0.0	0.0	0.004
Abdominal pain	0.0%	0.0%	5.5%	0.05	28	0.0	0.0	0.004
Acute kidney injury	3.9%	5.2%	-3.9%	0.37	28	0.0	0.0	0.028
Anaemia	0.0%	1.7%	15.0%	0.31	180	0.0	0.0	0.153
Asthenia	2.0%	3.4%	7.0%	0.12	28	0.0	0.0	0.009
Dehydration	0.0%	0.0%	5.5%	0.00	28	0.0	0.0	0.000
Diarrhoea	3.9%	0.0%	16.1%	0.10	28	0.0	0.0	0.008
Fatigue	5.9%	0.0%	14.1%	0.12	28	0.0	0.0	0.009
Febrile neutropenia	13.7%	5.2%	-13.7%	0.39	28	0.0	0.0	0.030
Flatulence	0.0%	0.0%	5.5%	0.00	28	0.0	0.0	0.000
Hypercalcaemia	2.0%	5.2%	-2.0%	0.08	28	0.0	0.0	0.006
Hypokalaemia	2.0%	0.0%	5.3%	0.20	0.02	0.0	0.0	0.000
Hypophosphatemia	0.0%	0.0%	6.0%	0.07	28	0.0	0.0	0.005
Hypotension	0.0%	1.7%	9.1%	0.07	0.01	0.0	0.0	0.000
Nausea	0.0%	0.0%	5.5%	0.10	28	0.0	0.0	0.008
Neutropenia	43.1%	29.3%	-28.1%	0.15	28	0.0	0.0	0.011
Pneumonia	17.6%	15.5%	-2.6%	0.19	7	0.0	0.0	0.004
Sepsis	0.0%	0.0%	9.1%	0.20	28	0.0	0.0	0.015
Septic shock	0.0%	3.4%	5.5%	0.20	28	0.0	0.0	0.015
Syncope	0.0%	0.0%	9.1%	0.1	28	0.0	0.0	0.008
Thrombocytopenia	5.9%	10.3%	58.1%	0.31	28	0.0	0.0	0.024
Total	-	-	-	-	-	**0.0**	**0.0**	**0.035**

IsaPd – isatuximab in combination with pomalidomide and dexamethasone; Pd – pomalidomide and dexamethasone; PanVd – panobinostat, with bortezomib and dexamethasone

*Notes: * the rates for PanVd include the adjustments made by the company "reflecting the difference in the incidence of AEs for PanVd versus IsaPd" (clarification response, page 54).[7]*

ǂ - In the company's model, the average duration of each AE was converted to years.

§ - In the company's base case, AE-related QALY decrements for IsaPd and Pd are assumed to be zero.

4.2.4.4 Resource costs

The model includes costs associated with: (i) drug acquisition and administration; (ii) disease management; (iii) treatments following disease relapse/progression; (iv) management of AEs, and (v) end of life care. These costs are summarised in Table 9.

Table 9: Summary of costs applied in the company's model

Cost parameter	Base case analysis		Additional analysis
	IsaPd §	Pd	PanVd
Drug costs (per week, first cycles*)	[redacted]	[redacted]	[redacted]
Administration costs (per week, first cycles*)	[redacted]	[redacted]	[redacted]
Drug costs (per week, subsequent cycles*)	[redacted]	[redacted]	[redacted]
Administration costs (per week, subsequent cycles*)	[redacted]	[redacted]	[redacted]
Disease management – event-free (per week)	£38.73	£38.73	£38.73
Disease management – progressed disease (per week)	£38.73	£38.73	£38.73
Disease management – other costs (once-only)	£679.08	£660.01	£313.16
Subsequent treatment drug and administration costs (post-progression, once-only, applied to discontinuers in each cycle)	[redacted]	[redacted]	[redacted]
End of life care (once-only)	£894.15	£894.15	£894.15
Grade 3+ AEs (once-only)	£1,618.37	£1,156.19	£1,948.84

AE - adverse event; IsaPd – isatuximab in combination with pomalidomide and dexamethasone; PanVd - panobinostat, with bortezomib and dexamethasone; Pd – pomalidomide and dexamethasone.
*Notes: * For the first 4 weeks for IsaPd and 8 weeks for PanVd.*
§Includes PAS for isatuximab.

(i) Drug acquisition and administration costs

Drug acquisition and administration costs are modelled as a function of the mean body weight or BSA observed in ICARIA-MM,[11] the planned treatment schedule, relative dose intensity (RDI) and unit costs (Table 10). Treatment schedules involve a reduction in the number of days the drug is administered after the first 4 weeks of treatment, in the case of isatuximab in IsaPd. Based on its list price, the cost per pack of 100mg vial of isatuximab (1 days' supply) is [redacted]. The company has an agreed PAS which takes the form of a simple price discount of [redacted]; the discounted cost per pack of IsaPd is therefore [redacted]. In secondary analyses, the company has provided results that do not include confidential PAS discounts for other drugs, which is consistent with NICE guidance. Drug prices were taken from the electronic Market Information Tool (eMIT) and the British National Formulary (BNF).[46, 47]

The company has used the distribution of patients using 20mg/40mg and oral/IV dexamethasone in each treatment arm in ICARIA-MM to estimate the costs of dexamethasone as part of the IsaPd intervention and the Pd comparator. The costs of IsaPd also included premedication drugs, which included 1000mg of paracetamol, 50mg of ranitidine and 50mg of cetirizine being administered on the same days as isatuximab. The costs of Pd included the costs of acetylsalicylic acid for 21 days on the same days as pomalidomide.

Administration costs for each treatment are calculated assuming that only the highest cost of each treatment component would be applied in each cycle, and were based on NHS Reference Costs 2017/2018 (codes SB11Z to SB15Z).[35] Estimates for each treatment period for drug and administration costs are applied to patients on treatment in each cycle, obtained from the chosen TTD function estimated from data in ICARIA-MM.[11] The ERG notes that this is likely to introduce some inaccuracy as it will not take into consideration the exact timings of drug administration and treatment discontinuation.

The drug acquisition costs for PanVd were based on the SmPC for panobinostat;[28] and data from the PANORAMA-2 trial;[9] there is a dose reduction, for bortezomib and dexamethasone after the first 24 weeks of treatment and a maximum period of treatment of 48 weeks. The drug and administration costs for PanVd are calculated based on the TTD function for IsaPd, to which a fixed HR of [redacted], based on the unanchored MAIC is applied.

Table 10: Dosing, treatment schedules and drug cost per cycle for first-line treatments included in the company's model

Regimen	Regiment component	Administration route	Dosing schedule	RDI	Drug costs per week	NHS reference code	Administration costs per week
IsaPd	Isatuximab	IV	10mg/kg, 4 days/first 4 weeks; 10mg/kg, 2 days/subsequent periods of 4 weeks	[redacted]	[redacted]§	SB13Z (first dose); SB15Z (subsequent doses)	[redacted]
	Pomalidomide	Oral	4mg/day, 21 days/every 4 weeks	[redacted]	£2,221.00	SB11Z (first dose) *; none (subsequent doses)	£32.90(w1-4) */ £0 (w5+)
	Dexamethasone	Oral or IV	20 or 40mg/day, 4 days/ every 4 weeks	[redacted]	£15.41 (weighted)	None(first dose), SB15Z (subsequent IV doses), none (subsequent oral doses)*ǂ	£0.00*ǂ
	Premedication (Paracetamol, Ranitidine and Cetirizine)	IV	Paracetamol 1000mg, ranitidine 50mg and cetirizine 50mg on the same days as isatuximab	[redacted]	£0.58 (w1-4)/ £0.29 (w5+)	None(first dose), SB15Z (subsequent IV doses)*ǂ	£0.00*ǂ
Pd	Pomalidomide	Oral	4mg/day, 21 days/every 4 weeks	[redacted]	£2.221.00	SB11Z (first dose) *; none (subsequent doses)	£32.90(w1-4) */ £0 (w5+)
	Dexamethasone	Oral or IV	20 or 40mg/day, 4 days/every 4 weeks	[redacted]	£20.00 (weighted)	None(first dose), SB15Z (IV) (subsequent IV doses) †ǂ	£233.23ǂ
	Acetylsalicylic acid	Oral	325mg/day, 21 days/every 4 weeks	[redacted]	£0.10	SB11Z (first dose) *; none (subsequent doses)	£32.90(w1-4) */ £0 (w5+)
PanVd	Panobinostat	Oral	20mg/day, 6 days/every 3 weeks	72.9%	£1,552.00	none	£0.00
	Bortezomib	Injection	1.3mg/m^2, 4 days/every 3 weeks for the first 24 weeks; then 2 days/every 3 weeks for the subsequent 24 weeks	79.8%	£1,016.51 (w1-24)/ £508.25 (w25+)	SB12Z (first and subsequent doses)	£232.54 (w1-24)/ £116.27 (w25+)
	Dexamethasone	Oral	20mg/day, 4 days/every 3 weeks for the first 24 weeks; then 2 days/every 3 weeks for the subsequent 24 weeks	87.5%	£53.33(w1-24)/ £26.67	SB11Z (first dose) *; none (subsequent doses)	£43.87(w1-3) */ £0.0 (w4+)

*§Includes PAS for isatuximab. *The company uses only the highest value of administration costs for each treatment arm; therefore, the value is not actually used.† The administration costs of dexamethasone taking orally were costed as being £0.00 in all cycles.ǂ The ERG believes that there is an error in this calculation; please see Section 4.3.2 for more details.*

(ii) Disease management costs

Disease management costs are related to resource use for follow-up, monitoring and concomitant treatments available to patients throughout their disease, such as medical visits, blood tests and biochemistry, GCSF, red blood and platelet transfusions.

The costs within the model related to follow-up and monitoring (physician visits, complete blood count tests and biochemistry) use the assumed cost per cycle which is applied to the state occupancy for PFS and PPS. Unit costs for each of these interventions were based on the NICE technology appraisal for daratumumab (TA510),[36] updated by the company to 2017/2018 values, with the frequencies of visits based on clinical opinion and assumed to happen every month indefinitely independent of health state or treatment group.

The costs of concomitant treatments (GCSF, blood and platelet transfusions) are applied as once-only costs to all patients. The number of procedures received per patient and the rates of patients receiving each intervention for IsaPd and Pd patients are based on data from ICARIA-MM,[7, 11] whilst these values for patients receiving PanVd were based on NICE technology appraisals for daratumumab (TA510) and pomalidomide (TA427).[36, 53] Unit costs of these procedures were based on NHS Reference Costs 2017/2018.[35] Disease management costs used within the model for IsaPd, Pd and PanVd are summarised in Table 11.

The ERG notes some discrepancies between the revised values reported by the company for the rates of patients receiving GCSF, blood and platelet transfusions and the number of these procedures received per patient in the clarification response (clarification response B19, Table 20)[7] and the updated submitted model. Additionally, the ERG notes that these rates for patients receiving PanVd have changed between the original submission and the clarification with no reason provided. It is not clear which data were intended to be used by the company. The ERG has assumed that the values within the model are correct and has explored the impact of the alternative values on the ICER. As this impact was relatively small, less than £110 per QALY gained compared to Pd, and less than £500 per QALY gained compared to PanVd, the ERG used the values within the model and did not pursue this issue further. During the fact check process the company stated that "*Rates of patients receiving GCSF, blood and platelet transfusions and the numbers of these procedures received per patient for those receiving IsaPd and Pd were edited during the clarification process as recommended by the ERG. The values used are highlighted in clarification response B26. To allow for incorporation of different numbers of administrations by treatment, the model had been amended during the clarification process.*"

Table 11: Summary of health state resource use and costs (adapted from the company's updated model)

Resource	Rates for receiving concomitant treatments			Average interventions per patient (whole time horizon)			Frequency – all states (weekly)	Unit cost	Costs applied in the model*		
	IsaPd	Pd	PanVd	IsaPd	Pd	PanVd			IsaPd	Pd	PanVd
Physician visit	-	-	-	-	-	-	0.23014	£164.80	£37.90	£37.90	£37.90
Complete blood count test	-	-	-	-	-	-	0.23014	£2.51	£0.58	£0.58	£0.58
Biochemistry	-	-	-	-	-	-	0.23014	£1.11	£0.26	£0.26	£0.26
GCSF	10.3%	13.8%	20.0%	2.3	2.4	1	-	£52.70	£12.54	£17.45	£10.54
RBC transfusion	19.0%	41.4%	20.0%	1.8	2.8	3	-	£132.72	£45.31	£153.77	£79.63
Platelet transfusion	62.1%	50.0%	20.0%	4.3	4.2	4.79	-	£232.76	£621.23	£488.80	£222.98

EFS - event-free survival; IsaPd – isatuximab in combination with pomalidomide and dexamethasone; PanVd - panobinostat, with bortezomib and dexamethasone; Pd – pomalidomide and dexamethasone.

*Note: *Expressed as weekly costs for physician visits, complete blood count test and biochemistry and as once-only costs for GCSF, RBC and platelet transfusions.*

(iii) Costs of subsequent treatments (following disease relapse/progression)

The model includes the costs associated with treatments for relapse/progression after 4L treatment. Subsequent treatment included the ten treatments most frequently received by patients after progression in ICARIA-MM; the rates of patients receiving each treatment differ by treatment group, and are based on utilisation data for IsaPd and Pd patients from this study.[11] The company has assumed the same proportions for IsaPd would apply to PanVd patients in its secondary analyses.

The costs of post-relapse/progression treatment include drug acquisition and administration, which are based on unit costs from BNF, eMIT, NHS Reference Costs 2017/2018 and the average duration of treatment estimated from external data (Kantar Health Study of treatments in RRMM in Western Europe, NHS regimen information sheets, and a company's submission for PanVd (TA380)).[25, 33, 35, 46, 47, 49, 50, 54] These costs are summarised in Table 12, and are applied as a single cost to patients who discontinued treatment with IsaPd, Pd or PanVd in each cycle, irrespective of whether they have relapsed/progressed or died.

The ERG also notes that the company's clarification response states that according to clinical opinion, "*there were some differences in the post study treatments in ICARIA-MM vs UK clinical practice*" (clarification response, question B13).[7] However, the company states that "*These differences have been tested in the SA [sensitivity analyses]. The resultant ICER was £128,798 (with only PAS discount on isatuximab, a slight increase over the base case)*".

The ERG noted that thee was inconsistency in the proportion of people receiving daratumumab at 5L reported in the CS and used in the model. This was a potential concern as it appeared that the model may have used data for subsequent therapies from a later cut point than other outcomes such as OS. The ERG notified NICE of this on the 7th January 2020 but had not received a response from the company at the time of writing. The ERG has assumed that the values in the model are correct and comments that it is unlikely that the use of alternative figures would reduce the company's base case below £50,000 per QALY. As such, this has not been mentioned further within this report.

Table 12: Estimated costs of subsequent treatments (adapted from the CS, Tables 55 and 56, and the updated model)

Treatment	Rates for receipt subsequent treatments (IsaPd and PanVd)	Rates for receipt subsequent treatments (Pd)	Cost per pack	Drug Costs	Admin Costs	Total drug and administration costs (Isa and PanVd) *	Total drug and administration costs (Pd)*
Bendamustine	10.71%	11.90%	£75.13	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib	25.00%	16.67%	£762.38	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib	17.86%	21.43%	£1,056.00	[redacted]	[redacted]	[redacted]	[redacted]
Daratumumab	7.14%	38.10%	£1,440.00	[redacted]	[redacted]	[redacted]	[redacted]
Etoposide	10.71%	0.00%	£11.50	[redacted]	[redacted]	[redacted]	[redacted]
Thalidomide	3.57%	0.00%	£298.48	[redacted]	[redacted]	[redacted]	[redacted]
Lenalidomide	14.29%	2.38%	£4,368.00	[redacted]	[redacted]	[redacted]	[redacted]
Melphalan	10.71%	0.00%	£45.38	[redacted]	[redacted]	[redacted]	[redacted]
Panobinostat	3.57%	0.00%	£4,656.00	[redacted]	[redacted]	[redacted]	[redacted]
Pomalidomide	7.14%	7.14%	£8,884.00	[redacted]	[redacted]	[redacted]	[redacted]
Total	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]

IsaPd – isatuximab in combination with pomalidomide and dexamethasone; PanVd - panobinostat, with bortezomib and dexamethasone; Pd – pomalidomide and dexamethasone.
** Total costs after the application of the proportions of patients receiving each subsequent treatment.*

(iv) AE management costs

Costs related to the management of AEs are applied as once-only costs in the first model cycle, to all patients in each treatment group. Unit costs were estimated using NHS Reference Costs 2017/2018.[35] The frequency of events for IsaPd and Pd were obtained from data for 4L patients in the ICARIA-MM trial,[11] whilst the probabilities of having any of the AEs for PanVd were obtained from the company's submission to NICE for daratumumab's appraisal by NICE.[36] The frequencies, unit costs and estimates of costs due to AEs are presented in Table 13. The ERG notes that the mean duration of each AE, used in the estimates of AE-related utility decrements, was not directly accounted for when calculating these costs. Further, the unit costs used within the model did not match those reported within the CS (Table 54); the ERG was unsure of the reason for this discrepancy but believes that the choice of unit cost would not affect the ICER significantly.

Table 13: Frequency, unit costs and total costs associated with Grade ≥3 AEs (adapted from CS, Table 39, Appendix K.4, Table 57 and company's model)

Adverse event	Frequency of AEs			Unit costs	Total costs		
	IsaPd	Pd	PanVd		IsaPd	Pd	PanVd
Abdominal distension	0.0%	0.0%	7.3%	£2,490.55	£0.00	£0.00	£181.81
Abdominal pain	0.0%	0.0%	5.5%	£2,490.55	£0.00	£0.00	£136.98
Acute kidney injury	3.9%	5.2%	0.0%	£3,279.81	£128.62	£169.65	£0.00
Anaemia	0.0%	1.7%	15.0%	£575.01	£0.00	£9.91	£86.25
Asthenia	2.0%	3.4%	9.0%	£727.55	£14.27	£25.09	£65.48
Dehydration	0.0%	0.0%	5.5%	£0.00	£0.00	£0.00	£0.00
Diarrhoea	3.9%	0.0%	20.0%	£525.41	£20.60	£0.00	£105.08
Fatigue	5.9%	0.0%	20.0%	£727.55	£42.80	£0.00	£145.51
Febrile neutropenia	13.7%	5.2%	0.0%	£6,697.31	£919.24	£346.41	£0.00
Flatulence	0.0%	0.0%	5.5%	£0.00	£0.00	£0.00	£0.00
Hypercalcaemia	2.0%	5.2%	0.0%	£2,566.41	£50.32	£132.75	£0.00
Hypokalaemia	2.0%	0.0%	7.3%	£471.57	£9.25	£0.00	£34.28
Hypophosphatemia	0.0%	0.0%	6.0%	£471.57	£0.00	£0.00	£28.29
Hypotension	0.0%	1.7%	9.1%	£693.34	£0.00	£11.95	£63.02
Nausea	0.0%	0.0%	5.5%	£727.55	£0.00	£0.00	£39.68
Neutropenia	43.1%	29.3%	15.0%	£693.34	£299.09	£203.22	£104.00
Pneumonia	17.6%	15.5%	15.0%	£531.10	£93.72	£82.41	£79.67
Sepsis	0.0%	0.0%	9.1%	£3,005.41	£0.00	£0.00	£273.19
Septic shock	0.0%	3.4%	5.5%	£3,005.41	£0.00	£103.63	£165.30
Syncope	0.0%	0.0%	9.1%	£0.00	£0.00	£0.00	£0.00
Thrombocytopenia	5.9%	10.3%	64.0%	£687.95	£40.47	£71.17	£440.29
Total	-	-	-	-	**£1,618.37**	**£1,156.19**	**£1,948.84**

IsaPd – isatuximab in combination with pomalidomide and dexamethasone; Pd – pomalidomide and dexamethasone; PanVd – panobinostat, with bortezomib and dexamethasone

Notes: ǂ - In the company's model, the average duration of each AE was converted to years.

(v) End of life care costs

Costs related to terminal care were based on the NICE technology appraisal for pomalidomide (TA427),[53] and are also applied as once-only costs in the first model cycle to patients who died in any

cycle. The unit cost used by the company (£894.15) was derived from a scenario analysis which considered the distribution of patients who received care during the last week prior to death in a hospital setting, hospice, or used home services, and updated to 2017/2018 values.[3]

4.2.5 Model evaluation methods

The CS[3] base case presents incremental cost-effectiveness ratios (ICERs) for IsaPd versus Pd as a comparator. Results are presented using the deterministic and probabilistic versions of the model. The probabilistic ICERs are based on 1,000 Monte Carlo simulations. The ERG notes that the distributions used in the probabilistic sensitivity analysis (PSA) are not presented in the CS. Scrutiny of the model indicated that in generating sampled values the company used one of the following: modified 95% confidence intervals; bootstrapped data from the ICARIA-MM trial, or assumed that standard errors were assumed to be 25% of the mean, logged where appropriate. The ERG has identified limitations in the method used to generate sampled values for the health state utilities; these are discussed in further detail in Section 4.3.2. The results of the PSA are presented as a cost-effectiveness plane and as cost-effectiveness acceptability curves (CEACs) for IsaPd versus Pd.

Deterministic sensitivity analyses (DSAs) are presented for IsaPd versus Pd using tornado plots. Some of these analyses involve varying parameters according to their 95% CIs where available, or using +/- 25% of the expected value where 95% CIs were not available.

During the clarification process, pairwise ICERs and PSA results (cost-effectiveness planes and CEACs) were reported by the company for IsaPd versus PanVd for patients at 4L. DSAs using tornado plots for this comparison, results for IsaPd versus Pd using the ITT population in ICARIA-MM[11] (3L+) patients who received only 2 prior lines of treatment (3L) and patients with 3 or more prior lines of treatment (4L+) were not reported by the company using the updated model.[7] The ERG could produce these using the company's revised model but has not included these for brevity.

4.2.6 Company's model validation and verification

The CS (pages 169-170)[3] describes the company's model validation activities, which involved checking for errors, using different computers, comparing results of DSA and PSA against priors and point estimates, and testing the model on extreme values ("*pressure testing*"). The company states that an additional validation was conducted by an external agency, but no details were provided about which activities it involved, nor was supporting evidence presented regarding the outputs of these activities in terms of external validity.

4.2.7 Company's model results

The probabilistic and deterministic results presented in this section are based on the updated version of the company's model submitted in response to the clarification process; Table 14 presents the central estimates of cost-effectiveness generated using the company's model for the comparison of IsaPd versus Pd. For readability, the ERG has termed the results without an estimate of the PAS for drugs other than isatuximab as the company's base case. This is line with NICE guidance.

The probabilistic version of the updated model suggests that IsaPd is expected to generate an additional 1.63 LYs and 1.06 QALYs per patient compared to pomalidomide with dexamethasone; the corresponding ICER is £130,321 per QALY gained. The deterministic version of the model produces a lower ICER of £118,816 per QALY gained.

Table 14: Company's base case results - IsaPd versus Pd (based on the company's updated model and clarification response, discounted values)

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
Probabilistic model							
IsaPd	[redacted]	[redacted]	[redacted]	1.628	1.055	£137,519	**£130,321**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic model							
IsaPd	[redacted]	[redacted]	[redacted]	1.649	1.071	£127,267	**£118,816**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year IsaPd – isatuximab in combination with pomalidomide and dexamethasone; Pd – pomalidomide and dexamethasone; PanVd – panobinostat, with bortezomib and dexamethasone

The company presented the CEACs for IsaPd versus Pd in its clarification response (question B2, Page 31).[7] Assuming willingness-to-pay (WTP) thresholds of £30,000, and £50,000 per QALY gained, the company's model suggests that the probability that IsaPd generates more net benefit than Pd is 0.2%, and 1.6% respectively.

The company has not presented revised results for the deterministic univariate sensitivity analyses following the clarification process. However, the ERG comments that the ICER was only below £100,000 per QALY gained on two occasions, one when the RDI for pomalidomide in the Pd arm was increased by 50% and one where the RDI for isatuximab was reduced by 25%. The ERG notes that different assumptions used to model time-to-event data were not considered in this analysis.

Company's scenario analyses

In the initial submission, the company had undertaken several scenario analyses for IsaPd versus the Pd comparator, which are presented from pages 166 to 168 of the CS.[3] Although the results of these

analyses were not presented in the clarification response, they are present in the updated model provided by the company.[7]

The scenarios involved: not considering medication wastage in the model; using EQ-5D-5L utility values instead of 3L utilities; changing the proportion of patients receiving subsequent therapy and its mean duration based on expert opinion or previous HTA submissions; using expert opinion to estimate the mean duration of AEs; using survivor functions for modelling TTD, PFS and OS that would favour or disfavour IsaPd; assuming treatment discontinuation upon progression (using jointly-fitted lognormal or exponential distributions); using data from a previous STA[36] for some of the disease management costs; changing discount rates for outcomes and costs to 1.5%; assuming time horizons of 5, 10 and 20 years, and; using the weight distribution from the trial for dosage of isatuximab treatment. The company also presented extreme scenarios called 'favourable inputs' and 'unfavourable inputs', where all these modifications in the inputs, with the exception of the use of EQ-5D-5L utility values, were combined in order to result in the most favourable and unfavourable ICER for IsaPd.

Generally, most of the analyses produced ICERs that were similar to the company's base case scenario. However, scenarios that use distributions that would favour IsaPd (using a Weibull survival function fitted independently to each arm for TTD, and jointly-fitted RCS Weibull functions for PFS and OS) and consider no medication wastage, result in ICERs below £100,000 per QALY gained (£73,070 and £97,551 per QALY gained, respectively). In contrast, the scenarios that use unfavourable distributions for IsaPd (using a jointly-fitted log-logistic for TTD, jointly-fitted RCS lognormal for PFS and jointly-fitted lognormal for OS), assuming treatment discontinuation upon progression (using restricted lognormal distributions) and changing the time horizon length to 5 years, lead to ICERs above £150,000 per QALY gained (£196,696, £167,452 and £195,911 per QALY gained, respectively). The company also explored an alternative scenario using distributions based on expert clinical feedback (using jointly-fitted Weibull distributions for PFS and OS and maintaining the exponential distribution for TTD). This scenario results in an ICER for IsaPd versus Pd of £170,026 per QALY gained. The scenario that explores the most favourable combination of inputs for IsaPd results in the lowest ICER of these analysis (£55,158 per QALY gained), whilst the most unfavourable combination of inputs for IsaPd results in an ICER of £207,327 per QALY gained.

Company's additional analyses

The company has presented deterministic and probabilistic revised results for the pairwise comparison of IsaPd versus PanVd in its clarification response;[7] these are summarised in Table 15. IsaPd produces more LYGs and QALYs than Pd, at a lower cost. The ICER for IsaPd versus PanVd is higher than the base case analysis, estimated at £248,197 per QALY gained for the probabilistic analysis.

Table 15: Company's additional analysis results - IsaPd versus PanVd (based on the company's updated model and clarification response, discounted values)

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
Probabilistic model							
IsaPd	[redacted]	[redacted]	[redacted]	1.056	0.791	£196,393	**£248,197**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic model							
IsaPd	[redacted]	[redacted]	[redacted]	1.144	0.849	£184,053	**£216,856**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year IsaPd – isatuximab in combination with pomalidomide and dexamethasone; PanVd – panobinostat, with bortezomib and dexamethasone

The company has not presented revised results for the deterministic univariate sensitivity analyses following the clarification process. However, the ERG comments that the ICER for IsaPd versus PanVd is greater than £150,000 per QALY gained regardless any changes in the parameters investigated by the company. The ERG notes that different assumptions used to model time-to-event data were not considered in these analyses.

The scenario analyses for IsaPd versus the PanVd comparator produced similar results to those for the main analysis, whereby the use distributions that would favour IsaPd (using Weibull functions fitted independently to each arm for TTD, and jointly-fitted RCS Weibull functions for PFS and OS) results in ICERs of £153,572 per QALY gained, whilst changing the time horizon length to 5 years lead to an ICERs of £363,241 per QALY gained. The scenarios that explore the most '*favourable*' and '*unfavourable*' combinations of inputs for IsaPd compared with PanVd results in ICERs of £140,966 and £283,187 per QALY gained, respectively. The simultaneous use of clinician-selected survivor functions for OS (jointly-fitted Weibull) and PFS (jointly-fitted Weibull) results in an ICER for IsaPd versus PanVd of £310,241 per QALY gained.

4.3 Critical appraisal of the company's health economic analysis

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying health economic model upon which this was based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.

- Double-programming of the deterministic version of the company's model to fully assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any apparent errors in the implementation of the model.
- Examination of the correspondence between the description of the model reported in the CS[3] and the company's executable model.
- Re-running the PSA, DSAs and scenario analyses presented within the CS[3] and clarification response.[7]
- Where possible, checking of key parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

4.3.1 Adherence to the NICE Reference Case

The company's economic analysis is generally in line with the NICE Reference Case[55] (see Table 16). Each element is discussed in further detail within the ERG report.

Table 16: Adherence of the company's economic analyses to the NICE Reference Case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The company's health economic analysis is generally in line with the final NICE scope;[6] except that the population within the company's base case is narrower than specified within the scope (restricted to those at 4L). The company has provided supplementary analyses for 3L and 4L+ to comply with the scope. As noted in Section 2.3.2, the company has not yet been granted an EU marketing authorisation for IsaPd in this indication.
Comparator(s)	As listed in the scope developed by NICE	The NICE scope[6] specifies two comparators: Pd and PanVd. The company's base case focusses on Pd as the comparator; nevertheless, the company undertook an exploratory analysis of IsaPd compared with PanVd "*in order to meet the requirements of the scope*".
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Direct health effects for patients were used. Health impacts on caregivers were not included in the analysis.
Perspective on costs	NHS and PSS	The analysis adopts an NHS and PSS perspective. However, scrutiny of the model indicates that no PSS costs have been included in the company's model.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The results of the analyses are presented in terms of the incremental cost per QALY gained for IsaPd versus Pd (and IsaPd versus PanVd in additional analysis). The company has also chosen to present results in terms of cost per LYG.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 15-year time horizon. Approximately 97.5% of patients have died in the IsaPd group and 100% in the Pd group by the end of the modelled time horizon (and 99.7% in the PanVd group).
Synthesis of evidence on health effects	Based on systematic review	Time-to-event outcomes (TTD, PFS and OS), HRQoL estimates and AE frequencies for patients receiving IsaPd and Pd are based on data from a subgroup of patients (4L) from ICARIA-MM study;[11] this was the key study included in the company's systematic review of clinical evidence. Health outcomes for patients who receive PanVd are based on the results of a MAIC and assumptions. HRQoL losses due to AEs for PanVd compared to IsaPd are based on published literature.

Element	Reference case	ERG comments
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health gains are valued in terms of QALYs. The ICARIA-MM RCT[4] recorded EQ-5D-5L values which were mapped to EQ-5D-3L values.[29]. A GEE regression model was fitted to the EQ-5D-3L data.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	HRQoL gains were directly reported by patients.
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	The company applied the UK EQ-5D tariff to the derived EQ-5D-3L data.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource costs include those relevant to the NHS. Unit costs were valued at 2017/18 prices with drug costs set at 2019 prices.

AE - adverse event; CS - company's submission; EFS - event-free survival; ERG - Evidence Review Group; EQ-5D - EuroQoL 5-dimensions; HRQoL - health-related quality of life; ITT - intention-to-treat; OS - overall survival; PSS - Personal Social Services; QALY - quality-adjusted life year

4.3.2 Main issues identified within the critical appraisal

In general, the ERG believed the revised model structure and the parameter values used were appropriate for the decision problem. However, some limitations were identified. Box 1 summarises the main issues identified within the ERG's critical appraisal of the company's economic analyses. These issues are discussed in further detail in the subsequent sections.

Box 1: Main issues identified within the critical appraisal undertaken by the ERG

(1) Identification of model errors
(2) The time horizon is too short to capture all of the gains associated with IsaPd treatment
(3) Lack of reporting of sensitivity analyses relating to the functions used to model time-to-event data
(4) Potentially inaccurate estimation of drug acquisition and administration costs
(5) That drugs assumed to be used in 5L would not be used in England
(6) Potential face validity violations in the utilities sampled within the PSA
(7) Underestimation of uncertainty
(8) Uncertainty in the clinical evidence

(1) Identification of model errors

Incorrect formulae applied in relation to QALY losses at the end of life

Within the company's model, the QALY decrement associated with reduced HRQoL at the end of life is applied incorrectly as the negative value is subtracted rather than added to overall QALYs. This error would slightly decrease the ICERs of IsaPd compared with Pd and PanVd when amended.

Incorrect application of administration costs associated with dexamethasone

Within the model, the company weighted the costs of dexamethasone to take into consideration the proportion of patients receiving this drug intravenously and those receiving it orally. However, this was not taken into account when calculating the average administration costs. Incorporating the weighting reduces the costs associated with Pd, but has no impact on the costs of IsaPd as only the highest administration cost was assumed. Accordingly, the ICER for IsaPd compared with Pd increases.

(2) The time horizon is too short to capture all of the gains associated with IsaPd treatment

The company's base case uses a time horizon of 15 years at which point 2.5% of modelled patients in the IsaPd group are alive, 0.3% in the PanVd group and 0.1% in the Pd. The additional QALYs accrued by these patients would not be included in the company's base case and the ICERs for IsaPd compared with Pd and PanVd would decrease.

(3) Lack of reporting of sensitivity analyses relating to the functions used to model time-to-event data

Whilst the model has the functionality to use different survival distributions to model time-to-event data (TTD, PFS and OS), the reporting of the impact of the use of alternatives on the ICER is lacking. The ERG would have preferred to see the results reported using a more extensive range of alternative time-to-event models.

(4) Potentially inaccurate estimation of drug acquisition and administration costs

The time cycle within the company's model (one-week) is shorter than the frequency at which treatments are provided, for example, isatuximab which is given fortnightly after the first four weeks. Within its model the company calculated an average weekly cost rather than explicitly incorporating isatuximab costs every fortnight, as such, drug costs are artificially reduced by people discontinuing in the week that a treatment is provided, as the second weekly costs would not be used. The ERG believes that amending this assumption would increase the ICERs of IsaPd compared with Pd and PanVd.

(5) Drugs assumed to be used in 5L that would not be used in England

Within the ICARIA-MM RCT,[4] patients who progressed received treatments that are not recommended in England, for example, daratumumab, or that clinical advice to the ERG suggested would be rarely used, for example, lenalidomide. The ERG does not know how the ICERs of IsaPd compared with Pd and PanVd would change were the costs and benefits of such treatments removed.

(6) Potential face validity violations in the utilities sampled within the PSA

Within the PSA it was possible that the sampled mean utility for patients in progressed disease could be higher than that for patients in PFS; the ERG does not believe this to be plausible. The ERG believes that amending this limitation is unlikely to affect the central estimate of the ICERs of IsaPd compared with Pd and PanVd.

(7) Underestimation of uncertainty in the decision problem

The ERG notes that it is likely that the uncertainty within the decision problem has been underestimated. Factors contributing to this include: (1) several AEs that are included in the model without allowing for parameter uncertainty; (2) several parameter values are set at zero, which implies that it is known that the AEs do not occur in the population of patients treated with the particular treatment in question; (3) whilst the model includes AEs for which Grade 3 or higher events were reported in at least 5% of the patients in any of the treatment arms of ICARIA-MM or for the relevant pivotal trials of the key comparators it is not clear what impact rare but important adverse events may have on the results; (4) that the duration of AEs is specified to be known without any uncertainty; and (5) duration of 5L

treatments were estimated from an external source. The ERG believes that amending these limitations is unlikely to affect the central estimate of the ICERs of IsaPd compared with Pd and PanVd.

(8) Uncertainty in the clinical evidence

The ERG comments that the comparison of efficacy between IsaPd and PanVd had to be conducted using an MAIC which will, as acknowledged by the company, have inherent limitations, primarily in ensuring that the matching undertaken is appropriate and that no unobserved confounders exist. In addition to this the company assume: that the treatment effect was constant over time, no interaction between treatment and line of therapy; and apply a hazard ratio to a non-proportional hazards model. The fact that ICARIA-MM was open-label may have introduced measurement bias, and may have altered patterns of oral medication use. The use of a post hoc group to generate the relative efficacy of IsaPd compared to Pd would not have the protection of randomisation, however, as baseline demographics and clinical characteristics were similar between the 4L patients and the full population and clinicians did not believe the relative efficacy to differ by line of treatment the analyses were believed suitable for decision making.

4.4 ERG's exploratory analyses

This section presents the methods and results of the ERG's exploratory analyses undertaken using the company's model.

4.4.1 Overview of the ERG's exploratory analyses

The ERG undertook exploratory analyses to address the key points identified within the critical appraisal (Section 4.3.3). These included correcting the errors identified in the company's model and amending assumptions. The exploratory analyses were combined to form the ERG's preferred base case analysis.

The ERG also undertook additional sensitivity analyses using the ERG's preferred base case model to explore the impact of: adopting different survival models for OS, PFS and TTD; assuming no drug wastage; and assuming 100% RDI for all 4L drugs.

Implementation of the ERG's exploratory analyses was repeated by a second member of the ERG to ensure that the results are free from errors. Technical details regarding the implementation of these analyses in the company's model are presented in ERG Appendix 1.

4.4.2 ERG exploratory analysis – methods

ERG preferred base case analysis

The ERG's preferred base case analysis is comprised of two sets of amendments to the company's model; these are detailed below.

ERG exploratory analysis 1: Correction of perceived error within the company model

The ERG made corrections to the company's model, by: (i) changing the formulae in each of the intervention and comparators' calculations worksheets such that the negative QALY values associated with deteriorating health at the end of life are added rather than subtracted from the overall QALY gains; and (ii) amending the formulae used to calculate dexamethasone administration costs for IsaPd and Pd to reflect the weighting between IV and oral administration.

ERG exploratory analysis 2: Extending the time horizon of the model

The ERG explored the impact on the ICER of extending the time horizon to 20 years which was the maximum time horizon within the model. At this point 0.7% of patients were alive in the IsaPd group and 0.0% alive in the Pd and PanVd groups.

ERG exploratory analysis 3: ERG's preferred base case

The ERG's preferred base case includes ERG exploratory analysis 1 and 2.

Additional sensitivity analyses using the ERG preferred model

The following additional sensitivity analyses were undertaken using the ERG's preferred model ("ERG exploratory analysis 3: ERG's preferred base case"). It is acknowledged that many functions could be used when fitting the data; for brevity, the ERG has selected two distributions which had relatively low BIC values and which have different properties in terms of hazard rates across time to provide an indication of the range of uncertainty within the ICER.

ERG additional sensitivity analysis 1: Use of alternative models for OS

Based on similar BIC values, see Figure 5, in Section 4.2.4.2.1, the ERG assessed the impact on the ICER if the jointly-fitted lognormal or the jointly-fitted Weibull distributions were used instead of the exponential distribution for OS.

ERG additional sensitivity analysis 2: Use of alternative models for TTD

Based on similar BIC values, see Figure 13, in Section 4.2.4.2.3, the ERG assessed the impact on the ICER if the jointly-fitted log-logistic or the jointly-fitted Weibull distributions were used instead of the exponential distribution for TTD.

ERG additional sensitivity analysis 3: Use of alternative models for PFS

Based on clinical advice provided to the company, the ERG assessed the impact on the ICER if the exponential or the jointly-fitted Weibull distributions were used instead of the jointly-fitted lognormal distribution for PFS. The ERG notes that the BIC for the jointly-fitted Weibull distribution, see Figure 9, in Section 4.2.4.2.2, is approximately seven more than the jointly-fitted lognormal, as such, the jointly-fitted Weibull model may not fit the observed data as well as the jointly-fitted lognormal.

ERG additional sensitivity analysis 4: No wastage considered

The ERG explored the impact of assuming no drug wastage.

ERG additional sensitivity analysis 5: Setting all RDIs to 100%

The ERG explored the impact of assuming that all reductions in dose intensities were not pre-planned and were associated with drug wastage. The ERG acknowledges that this sensitivity analysis is extreme but believes it provides useful information to the committee.

Limitations not amended by the ERG

The company's model is subject to a number of limitations which impact on the reliability of the ICERs generated from it. The following aspects of the model were not amended by the ERG:

Limitation 1: Potentially inaccurate estimation of drug acquisition and administration costs

The ERG did not have time to adjust the model to ensure that the costs of drug acquisition and administration related to the number of people who would receive the drug. The ERG anticipates that amending this error would slightly increase the ICER for IsaPd.

Limitation 2: Drugs assumed to be used in 5L that would not be used in England

The ERG acknowledges that the survival of patients may be influenced by the drugs that were used in 5L, as such removal of these costs without adjusting survival would be inappropriate. The ERG cannot predict with confidence the impact on the ICER for IsaPd if only drugs recommended in England were used in the ICARIA-MM study.

Limitation 3: Potential face validity violations in the utilities sampled within the PSA

The ERG does not anticipate that removing this limitation would markedly change the ICER but notes that the current sampling methodology is likely to increase the uncertainty within the PSA.

Limitation 4: Underestimation of uncertainty in the decision problem

The ERG did not have time to conduct further work to reduce the level of uncertainty. Whilst the ERG believes that it is likely there would be a small increase in the probabilistic ICER due to the increased uncertainty this cannot be predicted with certainty.

Limitation 5: Uncertainty in the clinical evidence

The ERG could not reduce the uncertainty in the clinical evidence.

4.4.3 ERG exploratory analysis – results

4.4.3.1 *IsaPd vs Pd*

ERG preferred base case analysis results

Table 17 presents the results of the ERG's preferred analysis. As shown in the table, correcting the errors in the company's deterministic model increases the ICER for from £118,816 to £126,611 per QALY gained, whilst increasing the time horizon to 20 years decreases the ICER to £115,996. The ERG's preferred probabilistic base case ICER for IsaPd versus Pd is estimated to be £133,461 per QALY gained.

Table 17: ERG exploratory analysis results: IsaPd vs Pd

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER
Company's base case							
IsaPd	[redacted]	[redacted]	[redacted]	1.649	1.071	£127,267	**£118,816**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 1: Correction of errors							
IsaPd	[redacted]	[redacted]	[redacted]	1.649	1.076	£136,269	**£126,611**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 2: Extending the time horizon to 20 years							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.098	£127,363	**£115,996**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic ERG preferred base case (ERG analyses 1 and 2 combined)							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.102	£136,364	**£123,769**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
Probabilistic ERG preferred base case (ERG analyses 1 and 2 combined) – 1000 iterations							
IsaPd	[redacted]	[redacted]	[redacted]	1.692	1.102	£147,041	**£133,461**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year

Table 18 details the results of the ERG's additional sensitivity analyses. The sensitivity analyses applied to the ERG-preferred base case resulted in an ICER range for IsaPd compared with Pd of £103,095 to £213,105 per QALY gained. The lower value of the range reflects a scenario in which no drug wastage is assumed, whilst the upper value of the range relates to the use of a jointly-fitted log-logistic model

for TTD. The ICER also appeared sensitive to the choice of survival model used for OS, although it was insensitive to the model used for PFS.

Table 18: ERG additional sensitivity analyses: IsaPd vs Pd (all deterministic)

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER
ERG's preferred base case							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.102	£136,364	**£123,769**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 1a: Use of a jointly-fitted lognormal model for OS							
IsaPd	[redacted]	[redacted]	[redacted]	1.701	1.108	£136,387	**£123,041**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 1b: Use of a jointly-fitted Weibull model for OS							
IsaPd	[redacted]	[redacted]	[redacted]	1.144	0.769	£135,279	**£176,028**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 2a: Use of a jointly-fitted log-logistic model for TTD							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.102	£234,792	**£213,105**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 2b: Use of a jointly-fitted Weibull model for TTD							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.102	£140,050	**£127,115**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 3a: Use of an exponential model for PFS							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.091	£136,364	**£124,987**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 3b: Use of a jointly-fitted Weibull model for PFS							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.080	£136,364	**£126,281**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 4: No wastage considered							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.102	£113,586	**£103,095**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 5: Setting all RDIs to 100%							
IsaPd	[redacted]	[redacted]	[redacted]	1.689	1.102	£148,663	**£134,932**
Pd	[redacted]	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year

4.4.3.2 *IsaPd vs PanVd*

ERG preferred base case analysis results

Table 19 presents the results of the ERG's preferred analysis for IsaPd versus PanVd. As shown in the table, correcting the errors in the company's model increases the ICER from £216,856 to £215,793 per QALY gained. The ERG's preferred base case ICER for IsaPd versus PanVd is estimated to be £238,300 per QALY gained.

Table 19: ERG exploratory analysis results, IsaPd vs PanVd

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER
Company's base case							
IsaPd	[redacted]	[redacted]	[redacted]	1.144	0.849	£184,053	**£216,856**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 1: Correction of errors							
IsaPd	[redacted]	[redacted]	[redacted]	1.144	0.853	£184,053	**£215,793**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 2: Extending the time horizon to 20 years							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.873	£184,140	**£210,812**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic ERG preferred base case (ERG analyses 1 and 2 combined)							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.876	£184,140	**£210,102**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
Probabilistic ERG preferred base case (ERG analyses 1 and 2 combined) – 1000 iterations							
IsaPd	[redacted]	[redacted]	[redacted]	1.104	0.825	£196,603	**£238,300**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year

Table 20 details the results of the ERG's additional sensitivity analyses. The sensitivity analyses applied to the ERG-preferred base case resulted in an ICER range for IsaPd versus PanVd of £141,814 to £365,613 per QALY gained. The lower value of the range reflects a scenario in which no drug wastage is assumed, whilst the upper value of the range relates to the use of a jointly-fitted log-logistic model for TTD. The ERG notes that in the latter analysis, the increase in treatment time for PanVd is curtailed by the maximum treatment duration of 48 weeks for this intervention. The ICER also appeared sensitive to the choice of model used for OS, although it was insensitive to the model used for PFS.

Table 20: ERG additional sensitivity analyses: IsaPd vs PanVd (all deterministic)

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER
ERG's preferred base case							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.876	£184,140	**£210,102**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 1a: Use of a jointly-fitted lognormal model for OS							
IsaPd	[redacted]	[redacted]	[redacted]	1.575	1.119	£184,925	**£165,233**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 1b: Use of a jointly-fitted Weibull model for OS							
IsaPd	[redacted]	[redacted]	[redacted]	0.789	0.633	£183,360	**£289,568**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 2a: Use of a jointly-fitted log-logistic model for TTD							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.876	£320,436	**£365,613**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 2b: Use of a jointly-fitted Weibull model for TTD							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.876	£189,351	**£216,046**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 3a: Use of an exponential model for PFS							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.853	£184,140	**£215,967**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 3b: Use of a jointly-fitted Weibull model for PFS							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.834	£184,140	**£220,920**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	
ERG sensitivity analysis 4: No wastage considered							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.876	£167,529	**£191,148**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG sensitivity analysis 5: Setting all RDIs to 100%							
IsaPd	[redacted]	[redacted]	[redacted]	1.181	0.876	£196,441	**£224,136**
PanVd	[redacted]	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year

The company does not believe that PanVd is a comparator in 4L treatment as it is rarely used due to toxicity reasons; as stated in Section 2.3.3 this opinion was not universally supported by the clinical advisors to the ERG.

The ERG notes that if a full incremental analysis was considered appropriate, PanVd dominates Pd and the ICER for IsaPd would be that compared with PanVd. On investigation, it was determined that the reason PanVd was assumed to be less expensive than Pd, despite providing more health gains, was that the estimated TTD was markedly lower on average in the PanVd arm compared with the Pd arm. However, the limitations of the MAIC need to be considered when evaluating the comparison of Pd and PanVd.

4.5 Discussion

The model submitted by the company was perceived to have few errors and therefore the deterministic ICERs for IsaPd compared with Pd were similar between the company's estimate (£118,816 per QALY

gained) and the ERG's estimate (£123,769 per QALY gained). Probabilistic analyses were seen to increase the ICER to £133,461 per QALY gained compared with Pd within the ERG's preferred base case. Sensitivity analyses indicated that the ICER for IsaPd compared to Pd was unlikely to be below £100,000.

The ICER for IsaPd compared with PanVd was higher than when Pd was the comparator; for this comparison, the deterministic ICERs were £216,856 per QALY gained (company) and £210,102 per QALY gained (ERG). Again, the probabilistic estimate was higher than the deterministic analysis; the ERG's estimate was £238,300 per QALY gained. Sensitivity analyses indicated that the ICER for IsaPd compared to Pd was unlikely to be below £140,000. However, there is considerable uncertainty in the ICER as the comparison was informed by a MAIC which may have multiple limitations. However, the ERG believes it highly unlikely that the cost per QALY would fall below £50,000 per QALY gained.

The appropriate ICER for IsaPd depends on whether it is believed that PanVd is an appropriate comparator; the company states that it is rarely used due to toxicity reasons. However, as stated in Section 2.3.3, there was mixed agreement amongst the clinical experts advising the ERG. If all treatments are considered appropriate then PanVd is expected to dominate Pd.

Finally, the ERG comments that these results do not include the PAS discounts for pomalidomide, panobinostat and lenalidomide and thus the ICERs presented here may be misleading. The cost per QALY gained for IsaPd compared with Pd and for IsaPd compared with PanVd when the PAS discounts are incorporated into the analysis are provided in a confidential appendix to this ERG report.

5 END OF LIFE

NICE end of life supplementary advice should be applied in the following circumstances and when both the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The following paragraphs summarise the evidence presented in the CS to support the company's position that IsaPd meets NICE's end of life criteria. Further information is provided in Table 32 of the CS.[3]

Short life expectancy criterion

In Table 32 of the CS,[3] the company cites precedent within NICE appraisals that the appraisal committee accepted that the end of life criteria were met when appraising pomalidomide (TA427)[26] at 3L and when appraising daratumumab (TA510) at 3L.[56] The company additionally states that the both Pd and PanVd have reported median OS times of less than 2 years. However, the ERG comments that the company's model predicted that the probabilistic (deterministic) estimate for mean survival for those on Pd was [redacted] years ([redacted] years). For patients receiving PanVd, these values were [redacted] ([redacted]) years. Given these values, it is not certain that the short life expectancy criterion is met.

Life extension criterion

In Table 32 of the CS,[3] the company states that "*Overall survival data are not yet mature. However, in the ITT population, at approximately 1 year of follow-up, a trend toward longer OS for IsaPd vs Pd alone, with an early separation of the survival curves (Figure 15), was observed (HR=0.687; [95% CI; 0.461, 1.023]).*

At the time of the analysis, the probability of surviving (95% CI) 12 months was 0.720 (95% C; 0.636, 0.787) in the IsaPd arm and 0.633 (95% CI; 0.545, 0.709) in the Pd arm." Based on the company's model, it is predicted that IsaPd will increase life expectancy by 1.628 years compared with Pd and by 1.056 years compared with PanVd, although the gain compared with PanVd is uncertain due to the comparison being informed by the MAIC. Given these values, the ERG agrees that it is likely that the criterion for extension to life is met.

6 OVERALL CONCLUSIONS

The main source of evidence in the CS was one open-label RCT of IsaPd for treating RRMM. Median PFS was greater in the IsaPd arm than the Pd arm among RRMM patients at 4L (HR 0.598 [95%: CI 0.348, 1.030], *p*=0.0611), and there was a trend towards superiority in OS in the IsaPd arm (HR 0.494 [95% CI 0.240, 1.015], *p*=0.0502), although the data were immature. IsaPd appears to be generally well tolerated. Whilst the study was generally well reported, there are limitations relating to its unblinded nature, post-hoc analysis of the 4L population and inconsistency between subsequent treatments in the study and in the current UK clinical management pathway.

IsaPd and PanVd were not part of a connected network of evidence and were compared using a MAIC of IsaPd from the ICARIA-MM study and PanVd from the PANORAMA-2 study. The results appeared favourable to IsaPd with a HR of 0.369 (95% CI 0.259 to 0.526) for PFS, and a HR of 0.642 (95% CI: 0.380, 1.082) for OS. As acknowledged by the company, the MAIC is subject to limitations; it is not clear whether the covariates represent all relevant prognostic factors and/or treatment effect modifiers and the final comparison may be biased. The company believes that PanVd is not an appropriate comparator as it is rarely used in 4L treatment due to its toxicity. As stated in Section 2.3.3 this view was not universally supported by clinical advice provided to the ERG. As such, the ERG believes that the company's secondary analyses will be appropriate for a proportion of patients who would receive PanVd rather than Pd.

The company submitted an economic model which indicated that the probabilistic cost per QALY gained of IsaPd compared with Pd was £130,321 and was £248,197 compared with PanVd. The ERG amended two perceived modelling errors and lengthen the time horizon from 15 years to 20 years. These amendments resulted in ICERs of £133,461 per QALY gained for IsaPd compared with Pd and of £238,300 per QALY gained for IsaPd compared with PanVd. Scenario analyses conducted by the ERG indicated that the ICER for IsaPd compared with Pd was unlikely to be below £100,000 and that the ICER for IsaPd compared with PanVd was unlikely to be below £140,000 per QALY gained. However, these values do not include PAS discounts related to pomalidomide, panobinostat or lenalidomide; results including these PAS discounts contained in a confidential appendix to this report.

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8. APPENDICES

Appendix 1: Technical appendix – instructions for implementing the ERG's exploratory analyses within the company's model

ERG exploratory analysis 1: Correction of errors

In the company's model:

(i) In worksheets 'Comp1 Calc', 'Comp2 Calc' and 'Comp3 Calc' of the company's model, replace the formula in cell FD29 with the formula "=IFERROR((DH29*IF(util.gp_apply="Yes",MIN(comp1.offtxPPS_util,FL29),comp1.offtxPPS_util)+SUM(DK29:INDEX(DK29:DK1072,util.term_duration))*comp1.term_util)*7/days_per_year,0)". Drag the formulae down to row 1072.

(ii) In worksheet 'Comp1 Calc', include in the end of the formulae in cells ED29, EE29, EF29 and EG29, respectively, the terms '*(0.745098039215686)*(1-0.135)', '*(1-0.745098039215686)*(1-0.135)', '*(0.745098039215686)*(0.135)', and '*(1-0.745098039215686)*(0.135)'. Drag each of these formulae down to row 1072.

(iii) In worksheet 'Comp2 Calc', include in the end of the formulae in cells EB29, EC29, ED29 and EF29, respectively, the terms '*1*0.155', '*0*0.155', '*1*(1-0.155)', and '*0*(1-0.155)'. Drag each of these formulae down to row 1072.

ERG exploratory analysis 2: Extending the time horizon of the model

In the company's model, go to worksheet 'Settings', cell H7, and replace value with "20".

ERG exploratory analysis 3: ERG's preferred base case

The ERG's preferred base case includes ERG exploratory analysis 1 and 2; therefore, apply all the changes listed above.

All sensitivity analyses undertaken by the ERG were applied separately to the ERG's preferred base case version of the model.

ERG sensitivity analysis 1: Use different functions to extrapolate OS data

In the company's model go to worksheet 'SelectDist_OS' and change all the curve selections in the dropdown menu in cells E9:G9, E10:G10 and E11:G11:

a. select, respectively, the options 'OS: IsaPd Lognormal (R)', 'OS: Pd Lognormal (R)' and 'OS: IsaPd Lognormal (R)'.

b. select, respectively, the options 'OS: IsaPd Weibull (R)', 'OS: Pd Weibull (R)' and 'OS: IsaPd Weibull (R)'.

ERG sensitivity analysis 2: Use different functions to extrapolate TTD data

In the company's model go to worksheet 'SelectDist_TTD' and change all the curve selections in the dropdown menu in cells E9:G9, E10:G10 and E11:G11:

a. select, respectively, the options 'TTD: IsaPd Log-Logistic (R)', 'TTD: Pd Log-Logistic (R)' and 'TTD: IsaPd Log-Logistic (R)'.
b. select, respectively, the options 'TTD: IsaPd Weibull (R)', 'TTD: Pd Weibull (R)' and 'TTD: IsaPd Weibull (R)'.

ERG sensitivity analysis 3: Use different functions to extrapolate PFS data

In the company's model go to worksheet 'SelectDist_PFS' and change all the curve selections in the dropdown menu in cells E9:G9, E10:G10 and E11:G11:

a. select, respectively, the options 'PFS: IsaPd Exponential', 'PFS: Pd Exponential' and 'PFS: IsaPd Exponential'.
b. select, respectively, the options 'PFS: IsaPd Weibull (R)', 'PFS: Pd Weibull (R)' and 'PFS: IsaPd Weibull (R)'.

ERG sensitivity analysis 4: Assumption of no drug wastage

In the company's model, go to worksheet 'Costs_MedAdmin', cell E6, and change the option in the dropdown menu to 'No'.

ERG sensitivity analysis 5: Assumption of all reductions in dose intensities were not pre-planned

In the company's model, go to worksheet 'Regimen', cells K9:K17, K19:K24 and K29:K34, and replace values with "100%".