Single Technology Appraisal

Isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]

Contents:

The following documents are made available to stakeholders:

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

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

2. **Clarification questions and company responses**

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

4. **Expert personal perspectives** from:
   a) Dr Jaimal Kothari - Consultant Haematologist, Clinical Expert, Sanofi
   b) Frances McGauran – Patient Expert, Myeloma UK

5. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group, University of Liverpool

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

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Isatuximab in combination with bortezomib, lenalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT)
[ID3981]

Document B

Company evidence submission

FINAL

06 December 2024

File name	Version	Contains confidential information	Date
ID3981_Isatuximab in combination for untreated MM_Document B_06Dec2024 [CIC redacted]	2.0	Yes	06 December 2024

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Abbreviations

ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANT	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem-cell transplant
ASH	American Society of Hematology
AST	Aspartate aminotransferase
AWMSG	All Wales Medicines Strategy Group
BCa	Bias-corrected and accelerated
BIM	Budget impact model
BM	Bone marrow
BOR	Best overall response
BSA	Body surface area
BSH	British Society of Haematology
CADTH	Canadian Agency for Drugs and Technologies in Health
CD38	Cluster of differentiation 38
CDC	Complement-dependent cytotoxicity
CDF	Cancer Drugs Fund
CDSR	Cochrane Database of Systematic Reviews
CE	Conformité Européenne
CEA	Cost-effectiveness analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CMA	Cost minimisation analysis
CMQ	Company MedDRA Queries
CO	Crossover
CR	Complete response
CRAB	hypercalcaemia, renal failure, anaemia, and bone impairment
CrCl	Creatinine clearance
CRd	Cyclophosphamide with lenalidomide and dexamethasone
CRO	Contract research organisation
CSR	Clinical study report
CT	Computed tomography
CTd	Cyclophosphamide with thalidomide and dexamethasone
CUA	Cost utility analysis
d	Dexamethasone
DALY	disability-adjusted life years
DRd	Daratumumab with lenalidomide and dexamethasone
DVMP	Daratumumab, bortezomib, melphalan and prednisone
DVTd	Daratumumab with bortezomib, thalidomide and dexamethasone

ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EHA	European Haematology Association
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer core quality of life 30-item questionnaire
EOT	End of treatment
EQ-5D	EuroQoL 5-dimensions
EQ-5D-5L	EuroQol-5 Dimensions-5 Level
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
Fc	Fragment crystallisable
FDA	Food and Drug Administration
FLC	Free light chains
FPI	First person in
FU	Follow-up
GCP	Good clinical practice
GHS	Global health status
GI	Gastrointestinal
HALY	Health adjusted life year
HCRU	Healthcare resource utilisation
HDT	High-dose therapy
HER	Health Electronic Health Record
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplant
HSUV	Health State Utility Index Value
HTA	Health technology assessment
HTAD	Health Technology Assessment Database
HUI	Health utilities index
Isa	Isatuximab
IADL	Instrumental activities of daily living
ICER	Incremental cost-effectiveness ratio
IF	Information fraction
Ig	Immunoglobulin
IgG	Immunoglobulin G
IMiD	Immunomodulatory agent
IMP	Investigational medicinal product
IMWG	International Myeloma Working Group
INAHTA	International HTA Database
IPCW	Inverse probability of censoring weighting
IPD	Individual-patient data
IPW	Inverse probability weighting
IQR	Interquartile range
IR	Infusion reaction

IRC	Independent review committee
IRT	Interactive response technology
IsaRd	Isatuximab, lenalidomide and dexamethasone
IsaVRd	Isatuximab, bortezomib, lenalidomide, and dexamethasone
ISS	International Staging System
ITC	Indirect treatment comparison
ITT	Intent-to-treat
IV	Intravenous
Ixa	Ixazomib
K	Carfilzomib
KRd	Carfilzomib, lenalidomide, dexamethasone
KTd	Carfilzomib, thalidomide, and dexamethasone
LDH	Lactate dehydrogenase
MAIC	Matching-adjusted indirect comparison
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	Monoclonal gammopathy of undetermined significance
MHRA	Medicines and Healthcare products Regulatory Agency
MM	Multiple myeloma
MP	Melphalan and prednisone
MPR	Melphalan, prednisone with Revlimid® (lenalidomide)
MPT	Melphalan, prednisone and thalidomide
MRD	Minimal residual disease
NA	Not applicable
NC	Not calculated
NCRAS	National Cancer Registration and Analysis Service
NDMM	Newly diagnosed multiple myeloma
NE	Not evaluable
NG	NICE Guidance
NGF	Next-generation flow
NGS	Next-generation sequencing
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIMP	Non-investigational medicinal product
NK	Natural killer
NMA	Network meta-analysis
NR	Not reached
ORR	Overall response rate
OS	Overall survival
Pan	Panobinostat
PBAC	Pharmaceutical Benefits Advisory Committee
pCODR	Pan-Canadian Oncology Drug Review
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PFS2	Progression-free survival on next line of therapy

PI	Proteasome inhibitor
PLD	Patient-level data
PO	Per os
POM	Pomalidomide
PPS	Post-progression survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
PSM	Partitioned survival model
PSS	Personal Social Services
PT	Preferred term
PY	Patient-year
Q4W	Every 4 weeks
Q	Quarter
QALY(s)	Quality adjusted life year(s)
QLQC30	EORTC Core Quality of Life questionnaire
QLQ-MY20	Myeloma module quality of life questionnaire
QoL	Quality of life
R	Lenalidomide
RBM	Results-based management
RCT	Randomised controlled trial
Rd	Lenalidomide and dexamethasone
R-ISS	Revised International Staging System
RMST	Restricted mean survival time
RR	Response rate
RRMM	Relapsed refractory multiple myeloma
RWE	Real-world evidence
S	Selinexor
SACT	Systematic Anti-Cancer Therapy
SAE	Serious adverse event
SC	Subcutaneous
sCR	Stringent complete response
SCT	Stem cell transplantation
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMM	Smouldering multiple myeloma
SmPC	Summary of product characteristics
SMQ	Standard MedDRA Queries
SOC	System Organ Class
SPM	Second primary malignancy
SUV	Standardised uptake value
T	Thalidomide
TA	Technology appraisal
Td	Thalidomide, dexamethasone
TE	Transplant eligible
TI	Transplant ineligible

TEAE	Treatment-emergent adverse event
TTBR	Time to best response
TTD	Time to treatment discontinuation
TTP	Time to progression
ULN	Upper limit of normal
V	Bortezomib
VAS	Visual analogue scale
VCd	Bortezomib with cyclophosphamide and dexamethasone
Vd	Bortezomib and dexamethasone
VGPR	Very good partial response
VMP	Bortezomib, melphalan and prednisone
VRd	Bortezomib, lenalidomide and dexamethasone
VTd	Bortezomib, thalidomide and dexamethasone

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

B.1.1 *Decision problem*

Isatuximab (Sarclisa, Sanofi) does not currently have a marketing authorisation in the UK for treating untreated multiple myeloma when a stem cell transplant is unsuitable; CHMP opinion is expected in [redacted] and MHRA marketing authorisation is expected in [redacted]. It has been studied in a clinical trial in people with newly diagnosed multiple myeloma who are ineligible for transplant. The trial compared isatuximab in combination with bortezomib, lenalidomide and dexamethasone with treatment with bortezomib, lenalidomide and dexamethasone (also known as VRd). The submission covers the technology's full anticipated marketing authorisation for this indication.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission
Population	Adults with untreated multiple myeloma when stem cell transplant is unsuitable	Adult patients with newly diagnosed active multiple myeloma who are ineligible for autologous stem cell transplant (ASCT)
Intervention	Isatuximab with bortezomib, lenalidomide and dexamethasone	Isatuximab, bortezomib, lenalidomide, and dexamethasone (IsaVRd)
Comparator(s)	• Daratumumab with lenalidomide and dexamethasone (DRd) • Lenalidomide with dexamethasone (Rd) • Bortezomib with alkylating agent and corticosteroid (such as cyclophosphamide and dexamethasone)	• Daratumumab, lenalidomide and dexamethasone (DRd) • Lenalidomide and dexamethasone (Rd) • Bortezomib, cyclophosphamide and dexamethasone (VCd) • Bortezomib, melphalan, and prednisone (VMP)
Outcomes	• Overall survival • Progression-free survival • Response rates • Time to treatment discontinuation • Minimal residual disease-negative status • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Response rates • Time to treatment discontinuation • Minimal residual disease-negative status • Adverse effects of treatment • Health-related quality of life

	Final scope issued by NICE	Decision problem addressed in the company submission
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	A cost-utility analysis was conducted to estimate lifetime costs and health-related outcomes, including incremental cost-effectiveness ratio (ICER) (cost per quality-adjusted life year [QALY]), from the perspective of the NHS and PSS, comparing IsaVRd to DRd, Rd, VCd, and VMP.
Special considerations including issues related to equity or equality	None specified in scope.	Transplant-eligible patients currently benefit from the quadruplet induction therapy of daratumumab plus bortezomib, thalidomide, and dexamethasone (DVTd) (TA763). In contrast, transplant-ineligible patients don't have access to the benefit of a quadruplet therapy. Access to IsaVRd therapy for TI patients would help mitigate this inequality.

Abbreviations: ASCT, autologous stem cell transplant; DRd, daratumumab, lenalidomide, and dexamethasone; DVTd, daratumumab, bortezomib, thalidomide, and dexamethasone; ICER, incremental cost-effectiveness ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; QALY, quality-adjusted life year; Rd, lenalidomide with dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

B.1.2 *Description of the technology being evaluated*

The summary of product characteristics (SmPC) is provided in Appendix C. The UK public assessment report of each component is not yet available.

Table 2: Technology being evaluated

UK approved name and brand name	Generic name: Isatuximab Brand name: SARCLISA
Mechanism of action	Isatuximab is an IgG1-derived monoclonal antibody that binds to a specific extracellular epitope of the CD38 receptor. CD38 is a transmembrane glycoprotein that is highly expressed on multiple myeloma cells (1). Isatuximab has multiple modes of action, including Fc-dependent immune mechanisms (ADCC, CDC, ADCP), Fc-independent direct apoptosis, inhibition of CD38 ectoenzyme activity, and immunomodulation, e.g. NK cell activation.
Marketing authorisation/CE mark status	CHMP opinion is expected in [redacted] MHRA marketing authorisation is expected in [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Isatuximab is indicated in combination with bortezomib, lenalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT)
Method of administration and dosage	Treatment administration consists of an induction period with IsaVRd and a continuous treatment period with IsaRd. The duration of each cycle in the induction period is 6 weeks (42 days) and a total of 4 cycles is planned. Induction therapy may be stopped in case of disease progression, unacceptable AE, patient's decision to discontinue, or completion of the induction period, whichever occurs first. After completion of induction on Cycle 4, participants enter the continuous treatment period from Cycle 5. The duration of each cycle during continuous treatment is 4 weeks (28 days). Treatment continues until disease progression, unacceptable AE, or participant's decision to discontinue. **Isatuximab** • 10 mg/kg intravenous (IV) infusion: o Cycle 1: Days 1, 8, 15, 22, and 29 o Cycle 2 to 4: Days 1, 15, and 29 o Cycle 5 to 17: Days 1 and 15 o Cycle 18 and thereafter: Q4W **Bortezomib** • 1.3 mg/m^2 subcutaneous (SC) injection: o Cycle 1 to 4: Days 1, 4, 8, 11, 22, 25, 29, and 32

	Lenalidomide
	• 25 mg PO:
	  ○ Cycle 1 to 4: Days 1–14 and 22–35 (10 mg/day for participants with CrCl ≥30 to <60 mL/min)
	  ○ Cycle 5 and thereafter: Days 1–21
	Dexamethasone
	• 20 mg IV on isatuximab infusion days, otherwise PO
	  ○ Cycles 1–4: Days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 (if ≥75 years old, given on Days 1, 4, 8, 11, 15, 22, 25, 29, and 32)
	  ○ Cycle 5 and thereafter: Days 1, 8, 15, and 22

Additional tests or investigations	Interference with serological testing Isatuximab binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). This interference with the indirect Coombs test may persist for at least 6 months after the last infusion of isatuximab. To avoid potential problems with RBC transfusion, patients being treated with isatuximab should have blood type and screen tests performed prior to the first infusion. Phenotyping may be considered prior to starting isatuximab treatment as per local practice. If treatment with isatuximab has already started, the blood bank should be informed. Interference with Serum Protein Electrophoresis and Immunofixation Tests Isatuximab may be detected on SPE and IFE assays used for monitoring disease monoclonal immunoglobulins (M-protein) and could interfere with accurate response classification. In patients with persistent very good partial response, where isatuximab interference is suspected, consider using a validated isatuximab-specific IFE assay to distinguish isatuximab from any remaining endogenous M-protein in the patient's serum, to facilitate determination of a complete response.
List price and the average cost of a course of treatment	• Isatuximab (Isa) IV (5.0 ml (vial) with 100mg/5ml: £506.94 (MIMS 2023) • Isatuximab (Isa) IV (25.0 ml (vial) with 500mg/25ml): £2,534.69 (MIMS 2023) Average weekly acquisition cost for IsaVRd: • Induction - £2,175.28 • Continuous (first year) - £1,864.64 • Continuous (after first year) - £932.71
Patient access scheme (if applicable)	The current PAS discount for isatuximab is [redacted].

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; ASCT, autologous stem cell transplant; CD38, cluster of differentiation 38; CDC, complement-dependent cytotoxicity; CE, Conformité Européenne; CHMP, Committee for Medicinal Products for Human Use; CrCl, creatinine clearance; Fc, fragment crystallisable; IFE, immunofixation; IgG1, immunoglobulin G1; Isa, isatuximab; IsaPD, isatuximab, pomalidomide, and dexamethasone; IsaRd, isatuximab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; IV, intravenous; MHRA, Medicines and Healthcare products Regulatory Agency; MIMS, Monthly Index of Medical Specialities; NK, natural killer; PAS, patient access scheme; PO, per os; Q4W, every 4 weeks; SC, subcutaneous; RBC, red blood cell; SmPC, summary of product characteristics; SPE, serum protein electrophoresis; UK, United Kingdom.
Source: Sarclisa SmPC (2).

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

B.1.3.1 *Disease overview*

Multiple myeloma (MM) is a rare and incurable haematological malignancy due to a single clone of antibody-secreting bone marrow plasma cells (3, 4). The uncontrolled, destructive growth of mutated plasma cells and the presence of abnormal monoclonal 'M' protein (also known as paraprotein) are key features of the pathophysiology of MM and the resultant symptoms, signs and clinical challenges (3, 5).

Most cases of MM are preceded by a more prevalent pre-malignant state called monoclonal gammopathy of undetermined significance (MGUS) (3). In a small subset of these patients, MGUS progresses to smouldering multiple myeloma (SMM) and then to active MM (5, 6). MM is characterised by bone loss and destruction rather than bone growth; this results in the release of growth factors which stimulate tumour growth and further promote bone loss (5). MM tumours can extend, invade or metastasize into extramedullary locations including the spleen, liver, and extracellular spaces in the later stage of the disease (3).

Patients with MM present with symptoms including hypercalcaemia, renal failure, anaemia, and bone impairment (CRAB); patients are also commonly prone to infections (6, 7). A high proportion of patients present with a complex and heterogenous profile that includes older age, underlying comorbidities, higher International Staging System (ISS) stage, or frailty (8-10).

Multiple myeloma remains incurable (11), with a median survival of less than 7 years (12). As MM is a progressive disease, the duration of remission is typically shorter after every subsequent relapse following intervention (13, 14). At diagnosis, the option of autologous stem cell transplant (ASCT) following high dose induction chemotherapy is recommended in patients who meet suitable criteria, inclusive of being considered fit enough to endure the treatment (15). However, approximately two-thirds of newly diagnosed patients with MM (NDMM) do not receive ASCT due to advanced age, poor performance status, or the presence of comorbidities or personal preference (16, 17).

B.1.3.2 *Epidemiology*

Compared with other cancers, myeloma is relatively rare. In the UK, myeloma is the 19th most common cancer, accounting for 2% of all cancer cases (18) which approximately

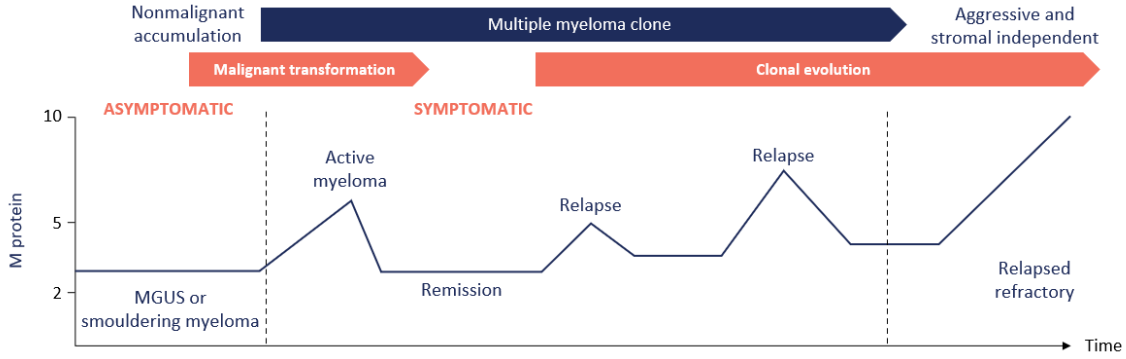
mirrors worldwide epidemiological disease statistics (19, 20). Most patients with MM are aged 65–74 years (8, 21). The median age at diagnosis is 72 years (22).

There are approximately 6,000 new cases of myeloma in the UK annually, with 5,316 reported in England in 2022 (18, 23). The incidence rate in the UK is 0.013% per year (16). The incidence rate of myeloma is predicted to rise by <1% in the UK between the 2023–2025 and 2038–2040 periods, which could result in approximately 8,300 incident cases of MM per year in 2038–2040 (18). Incidence rates of MM also differ by race, gender, and familial history of MM. MM is the most common haematologic malignancy in people of an African ethnic group in the US (24); the incidence rates for myeloma were 2.7–3.0 times higher for people of an African ethnic group in England compared with people of a white British, white Irish, and any other white background between 2013 and 2017 (25). Incidence rates are higher among males (4.9 per 100,000) than females (3.2 per 100,000) in the UK (24, 26). Individuals with a family history of MM have a higher risk of developing the disease compared with the general population. For those aged ≤63 years, the risk is 2.24 times higher (95% CI; 1.81, 2.75). For those aged >63 years, the risk is 1.96 times higher (95% CI; 1.72, 2.43) (27).

B.1.3.3 *The importance of effective first-line treatment in multiple myeloma*

Multiple myeloma is a progressive and relapsing disease, and the duration of remission typically becomes shorter at subsequent relapses, eventually leading to multi refractory disease and death (14, 28). Although the disease trajectory varies for each patient, the depth and duration of response diminish with every treatment line (14), leading to higher treatment discontinuation, worsening survival (Section B.1.3.4.1) and quality of life (QoL) outcomes (Section B.1.3.4.2), and higher healthcare system cost (Section B.1.3.4.3). The increased cost is largely due to an increase in hospital costs associated with relapses (29, 30). The typical disease trajectory illustrating the relapsing and remitting nature of MM, along with decreasing remission length is provided in Figure 1.

Figure 1: Disease trajectory of multiple myeloma



Abbreviation: MGUS, monoclonal gammopathy of undetermined significance.
Source: Adapted from Kurtin 2013 (14).

As a result of new anti-myeloma treatments, approaches, and supportive care, a large proportion of patients can now achieve complete response (CR). Consequently, newer response categories have been defined to identify responses deeper than those conventionally defined as CR, based on variables such as residual tumour cells in the

bone marrow (31). Deeper responses are associated with larger reductions in measurable disease and improved duration of response, with modern diagnostic and staging techniques such as minimal residual disease (MRD)-negativity now considered to be a marker of the deepest responses. A summary of deep response categories and definitions by International Myeloma Working Group (IMWG) consensus criteria is provided in Table 3.

Table 3: IMWG categories and response criteria for deep response

IMWG criteria	Definition
Standard IMWG response criteria†	
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis • Serum M-protein is reduced by ≥90% plus urine M-protein level <100 mg per 24 hours
CR	• Negative immunofixation on the serum and urine • Disappearance of any soft tissue plasmacytomas • <5% plasma cells in bone marrow aspirates
sCR	• Complete response as defined • Normal free light chain ratio** • Absence of clonal cells in bone marrow biopsy by immunohistochemistry (after counting ≥100 plasma cells)
IMWG MRD criteria (following CR)	
Sustained MRD-negative	• MRD negativity in the marrow confirmed more than 1 year apart • Confirmed by further evaluation (see below categories)
Flow MRD-negative	• Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow (or validated equivalent method) with a minimum sensitivity of ≥1 in 10^5 nucleated cells
Sequencing MRD-negative	• Absence of clonal plasma cells by NGS on bone marrow aspirate • The presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of ≥1 in 10^5 nucleated cells
Imaging-positive MRD-negative	• MRD negativity as defined by NGF or NGS • The disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT • Decrease to less mediastinal blood pool SUV • Decrease to less than that of surrounding normal tissue

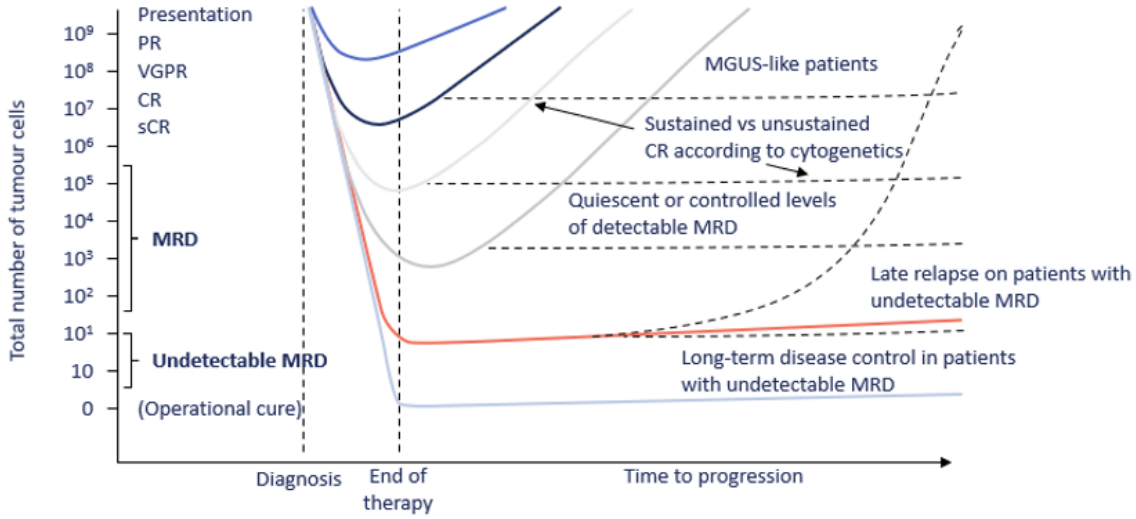
Abbreviations: CR, complete response; CT, computed tomography; IMWG, International Myeloma Working Group; MRD, minimal residual disease; NGF, next-generation flow; NGS, next-generation sequencing; PET, positron emission tomography; sCR, stringent complete response; SUV, standardised uptake value; VGPR, very good partial response.
† Partial response, minimal response, stable disease, and progressive disease categories have not been included.
Source: Adapted from Kumar 2016 (31).

With each relapse, the probability of resistant plasma cells (clones) appearing through acquired drug resistance from clonal evolution increases (32). The presence of resistant plasma cells during or following intervention is referred to as having the presence of MRD. This, along with therapy discontinuation due to treatment-related toxicity, is understood to be a major root-cause of relapse (33). MRD-negative status has been

cited as one of the most important predictors of long-term outcomes and is associated with improvements in progression-free survival (PFS) and overall survival (OS) (31, 34, 35). Another key driver in extending remission is not only achieving MRD-negative status but sustaining very low levels of MM cells, as per the table above (31). The association between depth of response to therapy and PFS is presented in Figure 2. It is well documented that the proportion of patients who achieve a deep response, decreases by line of therapy. In an observational study conducted in the Netherlands, 24% of patients achieved a very good partial response (VGPR) in the first line of therapy and 12% a CR, falling to 14% and 6%, respectively, in second line (36).

Optimising first-line treatment strategies is essential to prolonging remission, enhancing survival rates, and improving the quality of life of patients with MM. Early and effective intervention can help mitigate the challenges associated with multiple relapses due to disease progression and treatment resistance, ultimately leading to improved patient outcomes.

Figure 2: Hypothetical model to illustrate the association between response depth and PFS



Abbreviations: CR, complete response; MGUS, monoclonal gammopathy of undetermined significance; MRD, minimal residual disease; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
Source: Adapted from Paiva 2015 (34).

B.1.3.4 *Burden of multiple myeloma*

B.1.3.4.1 Clinical burden

Mortality due to MM is substantial. There were 3,098 deaths due to myeloma in the UK between 2017 and 2019 (37). The average annual number of deaths from myeloma is predicted to rise from approximately 3,600 (2023–2025 period) to approximately 4,500 (2038–2040 period) (37).

Multiple myeloma is a heterogeneous disease (38). Although some patients may have a more indolent clinical presentation/less aggressive disease, most patients will have substantial end-organ damage at diagnosis, well defined and clinically recognised by the CRAB features, as well as being prone to infections (6, 7, 39, 40). Other burdensome

symptoms and signs include pain, numbness, muscle weakness, and blood thickening (hyperviscosity) (39).

At diagnosis, clinical and disease heterogeneity can impact prognosis and treatment choices. Patients assessed as having high-risk myeloma, whether driven by ISS stage and/or cytogenetics, face substantially poorer outcomes (41). Certain cytogenetic abnormalities are associated with a poorer prognosis such as t(4;14), del(17/17p), t(14;16), t(14;20), non-hyperdiploidy, and gain(1q) (42).

When selecting a first-line treatment strategy, extensive evidence indicates that transplant-ineligible (TI) patients with MM have substantially shorter OS compared with those who are eligible for transplant (43-45). In a study of patients treated with drugs and therapies other than regimens available via the Cancer Drugs Fund (CDF) in England between January 2014 and August 2021, the median OS was not reached for patients who received first-line induction therapy followed by ASCT. In contrast, the median OS was only 29.60 months for patients who received first-line treatment without ASCT. This disparity is further highlighted in a real-world data study of 9,323 US patients with NDMM, which included 1,599 transplant-eligible (TE) and 7,724 TI patients. The adjusted hazard ratio (HR) for death in TI versus TE patients was 2.29 (95% CI; 2.01, 2.61; p<0.0001) objectively demonstrating the increased risk in the hazard of death for those patients not receiving a transplant (44). Additionally, a retrospective study comparing the OS of patients with MM found that TI patients had a significantly shorter OS (p<0.0001) than TE patients who had received ASCT or allogeneic SCT with 5-year survival of 38%, 70%, and 72%, respectively (45), again highlighting the disparity in OS outcomes between these two patient groups.

Survival rates also decline with each successive line of salvage therapy, as patients relapse. More specifically, from a UK perspective, a median OS of 44.5 months, 28.0 months, 17.6 months, and 11.5 months for patients receiving first-, second-, third-, and fourth-line treatment for MM, respectively, was seen initially in patients with NDMM treated with drugs other than regimens available via the CDF in England between 01 January 2014 and 31 August 2021, as per data from the Systematic Anti-Cancer Therapy (SACT) database (46). However, the introduction and routine use of newer treatments in clinical practice has been associated with improved outcomes. For instance, the median OS from diagnosis for patients with NDMM and treated with proteasome inhibitors and immunomodulatory drugs has improved over time, increasing from 5.5 years (2004–2008) to 7.3 years (2009–2013) (12). Although in recent years, newer combinations and novel anti-myeloma therapies often accessed via the CDF have been shown to further improve responses and survival, there are still unmet needs in relapsed patients as well as those newly diagnosed (refer to Section B.1.3.5.3).

Undergoing ASCT is still considered a standard of care intensive treatment for patients with NDMM and has been shown to result in the most durable responses at frontline with inclusion of maintenance therapy. However, it still leaves a considerable gap in the care and outcomes for the population of patients not receiving an ASCT (15, 16). A patient's eligibility for transplant is dependent on many factors including age, performance status, frailty, and the presence of comorbidities (47, 48). Consequently, approximately two-thirds of patients with NDMM do not receive ASCT (16, 17). The characteristics typically

associated with these patients, and the objective disparity in outcomes compared with those eligible for transplant, represent a diverse and difficult-to-treat population, and a continued unmet need for improved outcomes such as PFS that are closer to those seen in TE patients.

B.1.3.4.2 Humanistic burden

Following a diagnosis of MM, there is a substantial impact on the quality of life of patients and their caregivers.

Patients

The symptoms of MM, described in Section B.1.3.4.1, have a detrimental effect on patients' QoL. In studies in the UK, France, and Germany, patients with MM reported a high symptom burden, particularly fatigue and bone pain, which was strongly associated with reduced health-related quality of life (HRQoL) outcomes reported across both early and advanced stages of the disease (49-51). Patients with MM experience worse HRQoL than patients with acute myeloid leukaemia, chronic lymphocytic leukaemia, chronic myeloid leukaemia, Hodgkin lymphoma, and non-Hodgkin lymphoma (52).

Multiple myeloma has a more severe impact on QoL in TI than TE patients (53). Patients from several European countries experienced a substantial decline in independence and daily activity performance within the first 12 months post-diagnosis. Initially, pain intensity improved by month 3 but worsened by month 12, with TI patients consistently reporting higher pain levels than TE patients. The ability to manage daily activities independently decreased from 17% to 9%, and overall activity levels declined more sharply in TI patients compared with TE patients (53).

Mental health is also negatively impacted (54-56). Patients in a prospective population-based study reported concerns about their future health, with 37% expressing worry, 34% frequently thinking about their disease, and 21% fearing death (55). Patients with MM in the UK experience considerable mental health challenges, with 27.4% indicating signs of anxiety and 25.2% showing symptoms of depression, according to a cross-sectional survey (56). An online survey of myeloma patients (n=910) and carers (n=414) conducted in 2021, demonstrated the serious impact that a myeloma diagnosis had on patients' QoL, specifically their mental health (54). In 80% of patients, myeloma affected their mental health in some way, while 30% reported a major impact.

Patients who participated in discrete choice experiments have expressed a preference for treatments that are more efficacious and are willing to tolerate increased side effects with a therapy that can provide this benefit (57, 58).

Caregivers

Caring for patients with MM is a substantial QoL burden, which is rarely considered in cost-effectiveness analyses. As clinical management of MM is conducted in an outpatient setting, caregivers, rather than professional carers, provide most of the support needed (53, 59). Caring for a patient with MM is associated with stress and anxiety which can lead to a deterioration in the health of the caregiver (53, 56, 59).

According to evidence from a Myeloma UK study on the carer and family member experience, there is a substantial emotional, social, and practical impact associated with looking after a patient with MM (33). More specifically, 94% of carers are emotionally impacted, with the uncertainty being the major factor, and 84% of carers always put the needs of the patients with myeloma before their own needs. In total, 25% of carers in employment were unable to work or retired early due to caring for the patient with MM. Family and carers indicated that the perceived lack of control of their own lives, the change in the roles and/or responsibilities in the household, daily lifestyle changes, and missing out on important life events, are additional factors related to a myeloma diagnosis that impact their lives.

B.1.3.4.3 Economic burden

Direct medical costs, specifically for drugs and hospital admission, are the main drivers of the total cost of MM (60, 61). According to a study conducted in England which involved patients with myeloma and analysed English Hospital Episodes Statistics collected between 01 April 2014 and 31 March 2018, 90% of hospital admissions were elective but unplanned admissions accounted for 55% of the total hospitalisation cost (62).

Later lines of therapy are associated with increased costs vs first-line treatment, due to higher hospital and pharmacy costs (29, 30, 63, 64). For example, in a study investigating the economic burden of MM in the US, the monthly all-cause cost of treatment for MM was lowest in the first line of treatment compared with later lines (63). In 2015, the mean total healthcare costs of a single line of treatment for UK patients (n=56) with relapsed MM were €51,717 (£43,127[a]), with 95% attributed to the cost of drugs (65). Since the duration of first-line treatment is longest (63), and the rate of each type of visit increases at later lines of therapy (46), the selection of an optimal first-line therapy that prolongs the time to disease progression may reduce the overall economic burden of MM.

B.1.3.5 *Management of multiple myeloma*

B.1.3.5.1 Clinical guidelines

As per National Comprehensive Cancer Network (NCCN) Guidelines (Version 1.2025), preferred regimens for the first-line (primary) treatment of non-transplant candidates include IsaVRd (for patients <80 years old who are not frail), DRd, and VRd (66). Additional recommended regimens and regimens that are useful in certain circumstances are provided in Table 4. In general, the US, UK, European, and international guidelines align (47, 66-70).

[a] Euro value converted to GBP using a conversion of 1 EUR = 0.833908 GBP (27 September 2024) using online converter XE.com.

Table 4: NCCN guidelines for primary therapy in non-transplant candidates

Primary therapy for non-transplant candidates
In general, continue primary therapy until progression with de-escalation of therapy (modification of dose and duration) as needed.
Preferred regimens Daratumumab, lenalidomide, and dexamethasone (DRd) Isatuximab, bortezomib, lenalidomide, and de**xamethasone** (IsaVRd) (for patients <80 years old who are not frail) Bortezomib, lenalidomide, and dexamethasone (VRd)
Other recommended regimens Carfilzomib, lenalidomide, and dexamethasone (KRd)
Useful in certain circumstances Lenalidomide and low-dose dexamethasone (Rd) Bortezomib, cyclophosphamide, and dexamethasone (VCd) Bortezomib and dexamethasone (Vd) Bortezomib, lenalidomide, and dexamethasone (VRD-lite) for patients assessed as being frail Carfilzomib, cyclophosphamide, and dexamethasone Daratumumab, bortezomib, cyclophosphamide, and dexamethasone (DVCd) Isatuximab, carfilzomib, lenalidomide, dexamethasone (IsaKRd) Cyclophosphamide, lenalidomide, and dexamethasone (CRd)

Abbreviations: CRd, cyclophosphamide, lenalidomide, and dexamethasone; DRd, daratumumab, lenalidomide, and dexamethasone; DVCd, daratumumab, bortezomib, cyclophosphamide, and dexamethasone; IsaKRd, isatuximab, carfilzomib, lenalidomide, dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; NCCN, National Comprehensive Cancer Network; Rd, lenalidomide and low-dose dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; Vd, bortezomib and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone.
Source: NCCN Guidelines 2025 (66).

B.1.3.5.2 Clinical pathway of care in the UK

Daratumumab with lenalidomide and dexamethasone (DRd), Rd, and bortezomib- and thalidomide-based therapies have received positive NICE guidance (71-73).

NICE technology appraisals for TI patients with NDMM include:

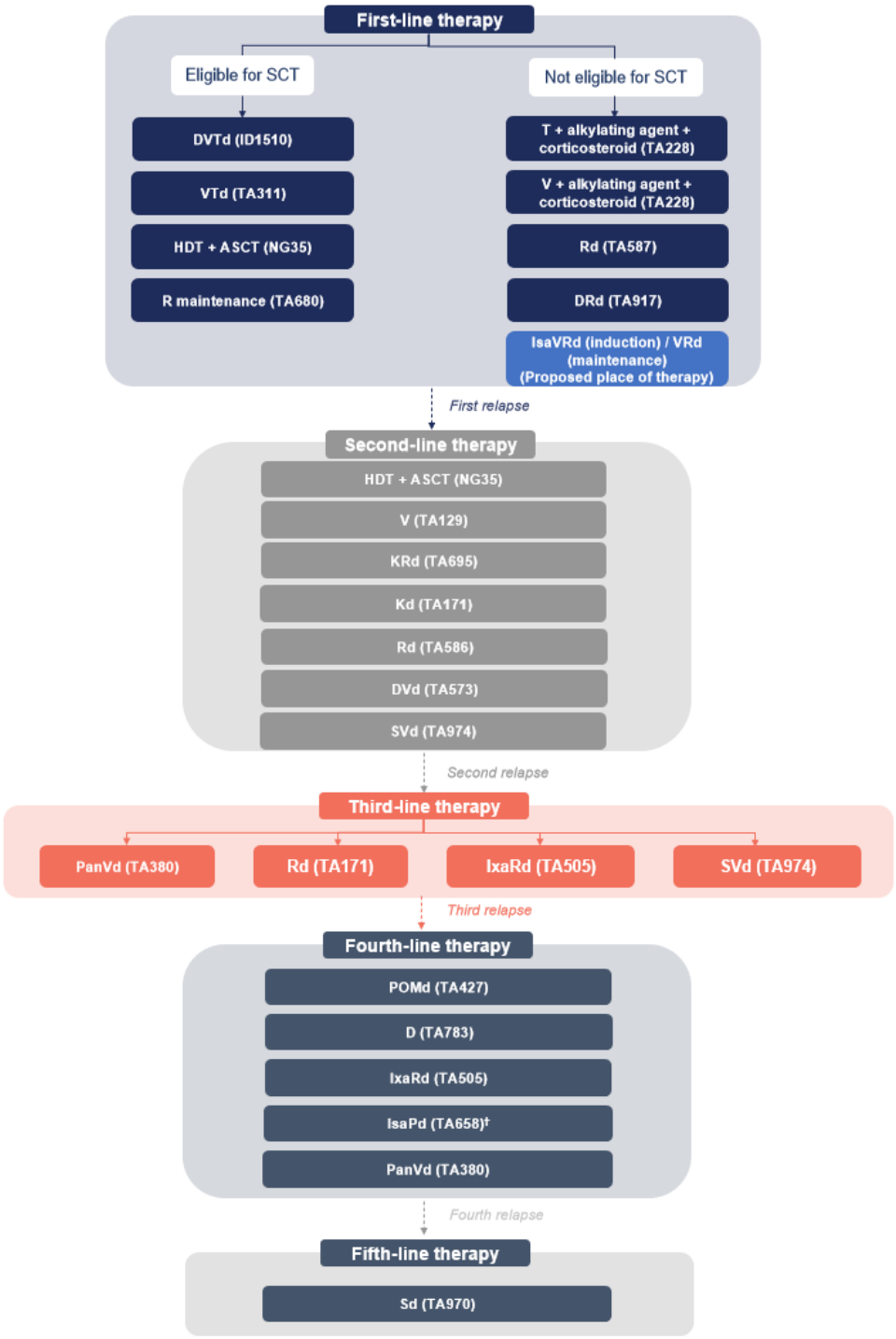
- Bortezomib and thalidomide for the first-line treatment of multiple myeloma (TA228) (71)
    - Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate
    - Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if:
        - high-dose chemotherapy with stem cell transplantation is considered inappropriate and

        - the person is unable to tolerate or has contraindications to thalidomide

- Lenalidomide plus dexamethasone for previously untreated multiple myeloma (TA587) (73)
    - Recommended as an option for previously untreated MM in adults who are not eligible for ASCT if thalidomide is contraindicated or not tolerated
- Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable (TA917) (72)
    - Recommended as an option for untreated MM in adults when ASCT is unsuitable

The current clinical pathway of care for patients with NDMM in the UK, along with the proposed positioning of isatuximab, bortezomib, lenalidomide, and dexamethasone (IsaVRd) as a first-line therapy is provided in Figure 3; the 1L treatment options for TI patients are listed on the right-hand side of the first box in the figure (48).

Figure 3: Current MM treatment pathway in England, as recommended by NICE, with anticipated positioning of IsaVRd



Abbreviations: ASCT, autologous stem cell transplant; CDF, Cancer Drugs Fund; d, dexamethasone; D, daratumumab; HDT, high-dose therapy; Isa, isatuximab; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; Ixa, ixazomib; K, carfilzomib; MM, multiple myeloma; NG, NICE Guidance; NICE, National Institute for Health and Care Excellence; Pan, panobinostat; POM, pomalidomide; R, lenalidomide; S, selinexor; SCT, stem cell transplant; T, thalidomide; TA, technology appraisal; V, bortezomib;.
† Note that this represents therapies that are routinely commissioned or available in the cancer drugs fund.
Source: Adapted from NICE guideline on diagnosis and management of myeloma [NG35] and lead team presentation for daratumumab monotherapy CDF review of TA510 (48).

In the final scope (Section B.1.1) provided by NICE (74), the comparators of interest for this submission include:

- Daratumumab with lenalidomide and dexamethasone
- Lenalidomide with dexamethasone
- Bortezomib with alkylating agent and corticosteroid (such as cyclophosphamide and dexamethasone)

However, it is worth noting that before the introduction of DRd, and as outlined in the final scope of TA917, the primary comparator was Rd, which accounted for approximately 70% of TI patients. According to TA917 and discussion during the decision problem meeting for this appraisal, DRd is expected to account for 65% of patients in 2024-2025 with clinicians estimating this figure to be currently as high as 80-90%, making it the main relevant comparator (16, 75).

For the purpose of this submission and to align with the scope, Sanofi considers the primary comparison to be between IsaVRd and DRd based on expert opinion. Additionally, comparisons are also provided for the other less relevant comparators which include Rd, VCd, and VMP.

B.1.3.5.3 The value of IsaVRd as a first-line treatment for non-transplant patients with NDMM

DRd has been the most recent recommendation by NICE as an option for untreated MM in adults when an ASCT is unsuitable (72). However, there is a need for a more efficacious first-line treatment for patients that can provide deep and durable responses early in the front-line setting to maximise the time patients are in remission. This is important as the progression to subsequent lines of therapy results in reduced responses to treatment, higher treatment discontinuation, and worsening survival and QoL outcomes (76, 77). In contrast to TE patients, TI patients reflect a diverse and difficult-to-treat population with a continued need for improved outcomes to achieve similar survival outcomes to TE patients.

The IMROZ clinical trial demonstrated a PFS benefit and consistent deep responses with first-line IsaVRd treatment compared with VRd therapy for adult TI patients with NDMM (Section B.2.6) (76). At 60 months, PFS was 63.2% in the IsaVRd group compared with 45.2% in the VRd group. Interim analysis showed that the addition of isatuximab to a VRd regimen resulted in a 40% lower risk of progression or death (HR: 0.60; [98.5% CI; 0.41, 0.88]; p<0.001).

Treatment with IsaVRd resulted in significantly more patients with MRD-negative status and a complete response vs VRd (55.5% vs 40.9%, respectively; p=0.003), MRD-negative status (58.1% vs 43.6%, respectively), sustained MRD-negative status for at least 12 months (46.8% vs 24.3%, respectively), and a complete or better response (74.7% vs 64.1%, respectively; p=0.01). The addition of isatuximab to VRd showed a favourable trend in OS for IsaVRd compared with VRd (HR: 0.776; [99.97% CI; 0.407, 1.480]; p=0.076); median OS was not reached in either group. These results were considered substantial by the clinical community, given the length of follow-up and the

fact that it is solely a first-line treatment. IsaVRd was shown to have a manageable safety profile, similar to current standard regimens.

A description of PFS and OS from pivotal/registration clinical trials of IsaVRd and current first-line treatments DRd, Rd, VMP, and VCd in TI patients with NDMM is provided in Table 5.

Table 5: Naïve comparison of PFS and OS for relevant comparators

	PFS		OS	
	Median (months)†	**60 Months (%)**	**Median (months)†**	**60 Months (%)**
IsaVRd	NR‡	63.2‡	NR‡	72.3‡
DRd	61.9§	52.5¶	90.3††	66.3¶
Rd	25.5–34.4‡‡, ¶	28.7¶	56.0–65.5§§, ¶	53.1¶
VMP	21.7–29.6†††, ‡‡‡	–	56.4§§§	46.0§§§
VCd	18.9¶¶¶	–	–	–

Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; NR, not reached; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone.
† This is a range of median values from multiple clinical trials.
‡ IMROZ (NCT03319667), Facon et al., 2024 (76).
§ MAIA (NCT02252172), Weisel et al., 2023 (78).
¶ MAIA (NCT02252172), Facon et al., 2021 (77).
†† MAIA (NCT02252172), Facon et al., 2024 (79).
‡‡ FIRST (NCT00689936), Benboubker et al., 2014 (80).
§§ SWOG S0777 (NCT00644228), Durie et al., 2020 (81).
††† VISTA (NCT00111319), San Miguel et al., 2008 (82).
‡‡‡ REAL-MM (NCT03829371), Larocca et al., 2023 (83).
§§§ VISTA (NCT00111319), San Miguel et al., 2013 (84).
¶¶¶ AMaRC 03-16 (ACTRN12617000202369), Mollee et al., 2021 (85).

Since there were no direct head-to-head clinical trials with comparator treatments, indirect treatment comparisons were conducted and indicated that IsaVRd offers statistically significant improvement in progression-free survival (PFS) compared with DRd, VMP, Rd, and VCd. Specifically, the constant HRs from matching-adjusted indirect comparisons (MAICs) were [redacted] for IsaVRd vs DRd [redacted] for IsaVRd vs Rd, and 0.20 (95% CI; 0.15, 0.26) for IsaVRd vs VMP. The HR from inverse probability weighting (IPW) results showed a statistically significant improvement in PFS for IsaVRd vs VCd with a HR of 0.34 (95% CI; 0.25, 0.47). For OS, a MAIC analysis comparing IsaVRd vs DRd showed a trend towards improvement with a HR of [redacted]. Statistically significant improvements in OS were observed in MAICs comparing IsaVRd vs Rd with a HR of [redacted] and IsaVRd vs VMP with a HR of 0.50 (95% CI; 0.37, 0.65). An IPW analysis comparing IsaVRd vs VCd showed a statistically significant improvement in OS with a HR of 0.48 (95% CI; 0.33, 0.69).

Disease control in the context of first-line therapy in patients with myeloma is crucial (86, 87). Therefore, as acknowledged in the literature and by clinical practice, early use of such efficacious regimens including an anti-CD38 agent is warranted (86). This is because the duration of response and median PFS progressively decrease with

successive lines of treatment. Early intervention offers each patient the best opportunity for durable disease control and improved survival.

IsaVRd combines all standard of care therapeutic classes including CD38 monoclonal antibody, immunomodulator, proteasome inhibitor, and corticosteroid in a combination therapy. This allows known synergistic anti-myeloma effects. The component drugs in the regimen are familiar to clinicians and manageable in current clinical practice as they are offered in other combination therapies in the UK.

The evidence provided in this dossier demonstrates that treatment with IsaVRd leads to a statistically significant and clinically meaningful improvement in PFS versus all standard of care treatments including DRd which can maximise the time patients are in this first remission, leading to better outcomes. It also leads to improved CR and MRD-negativity rates, demonstrating a substantial depth of response, whilst preserving a manageable toxicity profile (88).

Therefore, isatuximab in combination with bortezomib, lenalidomide and dexamethasone is intended for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for ASCT. The evidence provided in this dossier demonstrates that treatment with IsaVRd leads to a statistically significant and clinically meaningful improvement in PFS vs all comparators including DRd, which can maximise the time patients are in this first remission, leading to better outcomes. In addition, challenging some subgroups such as patients who present with high-risk may benefit from the addition of bortezomib component in this quadruplet regimen (47).

B.1.4 *Equality considerations*

TE patients currently benefit from the quadruplet induction therapy of daratumumab with bortezomib, thalidomide and dexamethasone (DVTd) (TA763). In contrast, TI patients do not have access to the benefits of a quadruplet, induction-type therapy before transitioning to reduced maintenance or continuous therapy. Access to IsaVRd therapy for transplant ineligible patients would help mitigate this inequality.

B.2. Clinical effectiveness

The addition of isatuximab to VRd led to a statistically significant and clinically meaningful improvement in PFS vs VRd alone, improved CR and MRD negativity, and a favourable OS trend

- IMROZ**,** a Phase III, prospective, multicentre, international, randomised, open-label, two-arm parallel group study, evaluates the addition of isatuximab to VRd in TI patients with NDMM (Section B.2.6.1)
- After a median follow-up of 59.73 months, IsaVRd demonstrated superior efficacy over VRd for PFS (Section B.2.6.1.1):
    - IsaVRd demonstrated a statistically significant reduction of 40.4% in the risk of death or disease progression compared with VRd (HR: 0.596 [98.5% CI; 0.406, 0.876], p=0.0005)

  - At 60 months, PFS was 63.2% in the IsaVRd group compared with 45.2% in the VRd group
  - PFS sensitivity analyses supported the primary result; a benefit was apparent in most subgroups
- IsaVRd demonstrated a statistically significantly higher proportion of patients with CR compared with VRd (74.7% vs 64.1%, respectively; p=0.008) (Section B.2.6.1.2)
- IsaVRd demonstrated a statistically significant improvement in MRD-negative status in patients with a CR at any time compared with VRd (55.5% vs 40.9%, respectively; p=0.0013) (Section B.2.6.1.2)
- IsaVRd demonstrated an improvement in the proportion of patients with “VGPR or better” compared with VRd (89.1% vs 82.9%, respectively; descriptive p=0.0259) (Section B.2.6.1.2)
- The addition of isatuximab to VRd showed a favourable trend in OS for IsaVRd compared with VRd (HR: 0.776; [99.97% CI; 0.407, 1.480]; p=0.076); median OS was not reached in either group
- IsaVRd improved time to progression compared with VRd (median not reached vs 59.70 months, respectively; HR: 0.414; [95% CI; 0.286, 0.598]), duration of response (median not reached vs 58.25 months, respectively), time to next treatment (median not reached vs 63.57 months, respectively; HR: 0.376; [95% CI; 0.265, 0.534]) and PFS2 (medians not reached; HR: 0.697; [95% CI; 0.51, 0.952]) (Section B.2.6.1.4)
- IsaVRd demonstrated an improvement in sustained MRD negativity for at least 12 months compared with VRd (46.8% vs 24.3%, respectively) (Section B.2.6.1.4)
- Subgroup analyses of CR, MRD negativity in CR, and VGPR or better, showed a positive treatment effect of IsaVRd over VRd for most subgroups (Section B.2.7.3)

Addition of isatuximab to VRd did not reduce QoL and was associated with a manageable tolerability profile

- The addition of isatuximab to VRd improved the QoL of the patient, as assessed using the EQ-5D-5L Health State Utility Index and mapped to 3L (Section B.3.4.6)
- The addition of isatuximab to VRd did not result in a detriment to the QoL of the patient, as assessed by the EQ-5D-5L Visual Analogue Scale or the QLQ-C30-Global Health Score (Section B.2.6.1.6)
- The IsaVRd safety profile was manageable in the IMROZ study, and consistent with the known safety profiles of each individual component of the regimen (Section B.2.10)
  - The percentage of patients with Grade ≥3 TEAEs was higher in the IsaVRd group (91.6%) compared with the VRd group (84.0%)

- IsaVRd rates of Grade ≥3 treatment-emergent adverse events (TEAEs) showed little difference with VRd (1.171 and 0.986 events per patient-year, respectively) once adjusted for exposure
- Grade 5 TEAEs were reported for 29 (11.0%) participants in the IsaVRd group and 10 (5.5%) participants in the VRd group
    - This difference was largely driven by the difference in treatment exposure (exposure-adjusted rates for Grade 5 TEAEs are 0.031 and 0.019 events per patient year with IsaVRd and VRd, respectively)
- IMROZ was conducted during the COVID-19 pandemic; in total, eight of the fatal TEAEs in the IsaVRd arm were related to COVID-19 compared with two in the VRd arm
- Fewer patients discontinued treatment on IsaVRd than VRd (22.8% vs 26.0%, respectively)
- The median relative dose intensities (RDIs) were similar in the IsaVRd and VRd groups for bortezomib (90.28% vs 86.65%, respectively), lenalidomide (77.74% vs 83.45%, respectively) and for dexamethasone (81.58% vs 79.34%); the median RDI of isatuximab was 93.58%

B.2.1 *Identification and selection of relevant studies*

B.2.1.1 *Clinical SLR*

B.2.1.1.1 Search strategy

A systematic literature review (SLR) was conducted in March 2021 to identify existing evidence on the efficacy, safety, and tolerability of approved and upcoming treatments for TE and TI patients with NDMM. The report was updated for the periods March 2021 to August 2022, July 2022 to August 2023, and July 2023 to April 2024.

The data sources used to identify the relevant studies included electronic databases and manual searching of conference proceedings. Bibliographies of key systematic reviews and meta-analyses were also screened to capture all relevant studies. Full details of the methodology used for the SLR including the search strategy, databases searched, and selection criteria are provided in Appendix D. Results for the latest update (July 2023 to April 2024) are presented in the main submission and results for all earlier search dates are included in Appendix D.

Although the SLR included data for TE and TI patients with NDMM, only data for TI patients are reported in this section, based on relevance for this submission.

B.2.1.1.2 Study selection

The PRISMA flow diagram for the 29 April 2024 update is presented Figure 4.

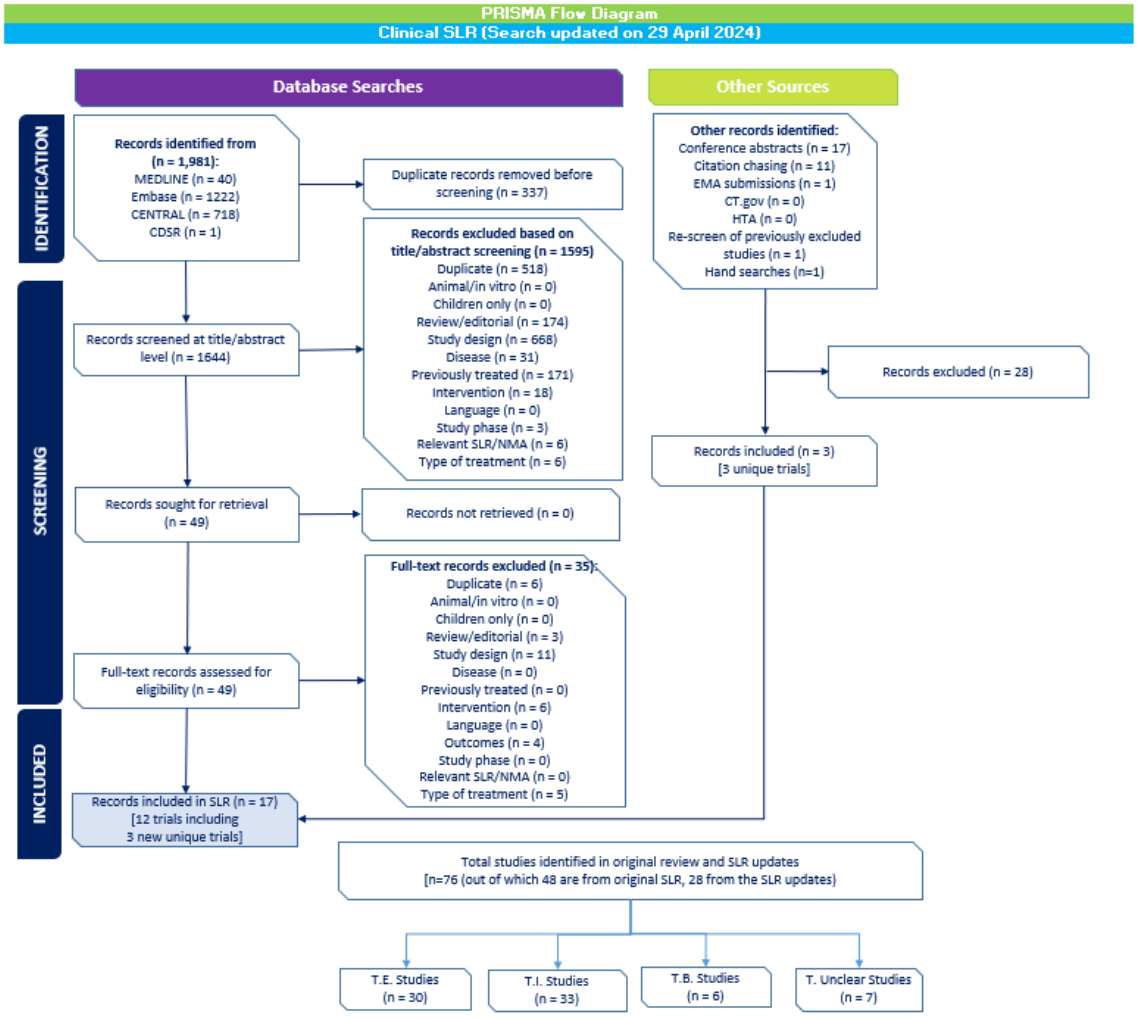
In the 2024 update (Figure 4), 1,981 records were identified from database searches. A total of 1,644 records were screened based on titles and abstracts after the removal of 337 duplicates records. Of these, 1,595 records were excluded. The full texts of

49 records were reviewed, and 35 records were excluded. Additionally, three records were included from the grey literature searches. In total, 17 references from 12 trials were included for the analysis. When combined with the RCTs from the original review and earlier updates, a total 76 RCTs were included.

Details of the study selection process and a complete list of included studies, along with the full list of excluded studies with the rationale for exclusion, are provided in Appendix D.

No clinical trials were identified in the clinical SLR that evaluated IsaVRd in patients who are ineligible for ASCT.

Figure 4: PRISMA Flow Diagram (SLR 2024 Update [29 April 2024])



Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review; T.B. or T. Unclear, studies including mixed population data or transplant status unclear; T.E., transplant-eligible NDMM patient population; T.I., transplant-ineligible NDMM patient population.
Source: Clinical SLR (89).

B.2.1.2 *Observational clinical SLR for VCd*

B.2.1.2.1 Search strategy

An SLR was conducted to identify all RCTs assessing the efficacy, safety, and tolerability of approved and upcoming treatments for patients with NDMM in both the TE and TI populations (Section B.2.1.1). When assessing the evidence base from the SLR for suitability for indirect treatment comparisons, only one study (AMaRC 03-16) was identified that compared VCd to DVCd. However, there were no PFS or OS data reported in AMaRC 03-16. Due to a lack of evidence for any direct or indirect comparison of IsaVRd with VCd and DVCd through RCT, a population-adjusted indirect comparison (PAIC) for IsaVRd with VCd and DVCd in the TI NDMM population was required. Therefore, a review of clinical evidence was conducted to collate non-randomised and observational studies assessing VCd/DVCd in TI patients with NDMM to support a PAIC.

The data sources used to identify the relevant studies included electronic databases and manual searching of conference proceedings. Searches were conducted from September 2023 onwards. Results from the original search and the most recent search update are presented in the main submission. Results of the individual searches are provided in Appendix D.2.1. Full details of the methodology used are provided in Appendix D, Section D.2.1.

Although the review included studies in both TI and TE patients, only data extraction and reporting were conducted for studies with a TI population.

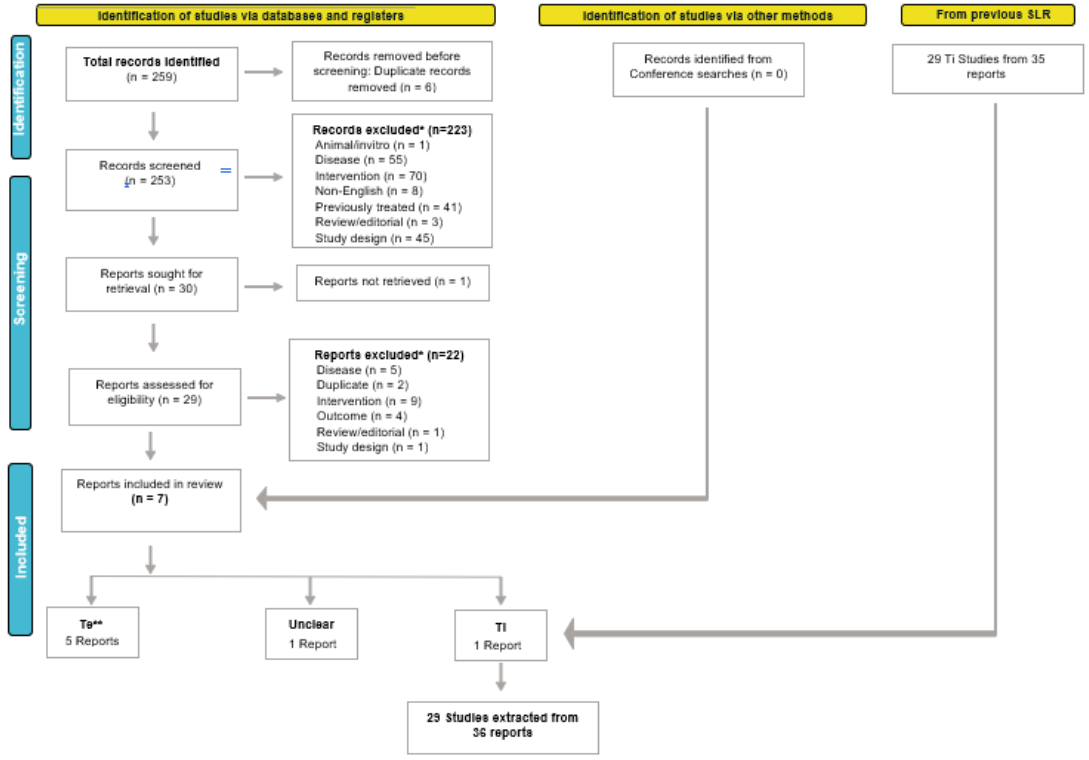
B.2.1.2.2 Study selection

The PRISMA flow diagram for the SLR is presented in Figure 5.

Across the SLR and update, a total of 29 studies were identified and VCd was assessed in 28 of the 29 included studies and one study assessed DVCd. Based on the current SLR findings, there are ten studies which are plausible candidates for PAIC and on initial review covering transplant-ineligibility, sample size, sufficient reporting of patient characteristics, and/or availability of relevant outcome data, the suitability of these individual studies for PAIC should be considered separately based on a detailed feasibility assessment plan.

Details of the study selection process and a complete list of included studies, along with the full list of excluded studies with the rationale for exclusion, are provided in Section D.2 of Appendix D.

Figure 5: PRISMA flow diagram (observational SLR, 2024)



Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review; Te, treatment-eligible NDMM patient population; Ti, treatment-ineligible NDMM patient population.
Source: Observational SLR (90).

B.2.2 *List of relevant clinical effectiveness evidence*

The systematic review of clinical evidence did not identify any RCTs of isatuximab in the population of interest to this submission (89).

The Phase III clinical trial (IMROZ) of isatuximab in patients with newly diagnosed multiple myeloma who are ineligible for transplant is included in this submission (Table 6; Sections B.2.2 to B.2.7). Interim results from this study (data from latest available cut-off point: 26 September 2023) are of relevance to this submission, as they provide evidence of the long-term efficacy and safety of isatuximab in the patient population of interest and informed the economic model for isatuximab. This study is anticipated to be completed by the end of June 2027. An overview of the clinical effectiveness evidence is provided in Table 7.

Table 6: List of relevant clinical evidence

Trial no. (acronym)	Population	Intervention	Comparator	Primary study ref(s)	Refs identified but not used further	Is study excluded from further discussion? If yes state rationale
IMROZ NCT03319667 Phase III RCT	Patients with newly diagnosed active multiple myeloma who are not eligible for ASCT or with no intent for ASCT as initial therapy	Active group IsaVRd	Control group VRd	CSR (88) Facon 2024 (76)	–	No (pivotal Phase III trial)

Abbreviations: ASCT, autologous stem cell transplant; CSR, clinical study report; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; RCT, randomised controlled trial; VRd, bortezomib, lenalidomide, and dexamethasone.

Table 7: Clinical effectiveness evidence for IMROZ

Study	**IMROZ (NCT03319667)**
Study design	Phase III, prospective, multicentre, international, randomised, open-label, two-arm parallel group study
Population	Patients with newly diagnosed multiple myeloma not eligible for transplant
Intervention(s)	IsaVRd
Comparator(s)	VRd
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	Not applicable
Reported outcomes specified in the decision problem	The outcome measures to be considered include: • Overall survival (OS) • Progression-free survival (PFS) • Response rates (CR and ≥VGPR rates) • Time to treatment discontinuation (TTD) • Minimal residual disease (MRD)-negative status • Adverse effects of treatment • Health-related quality of life (HRQoL)

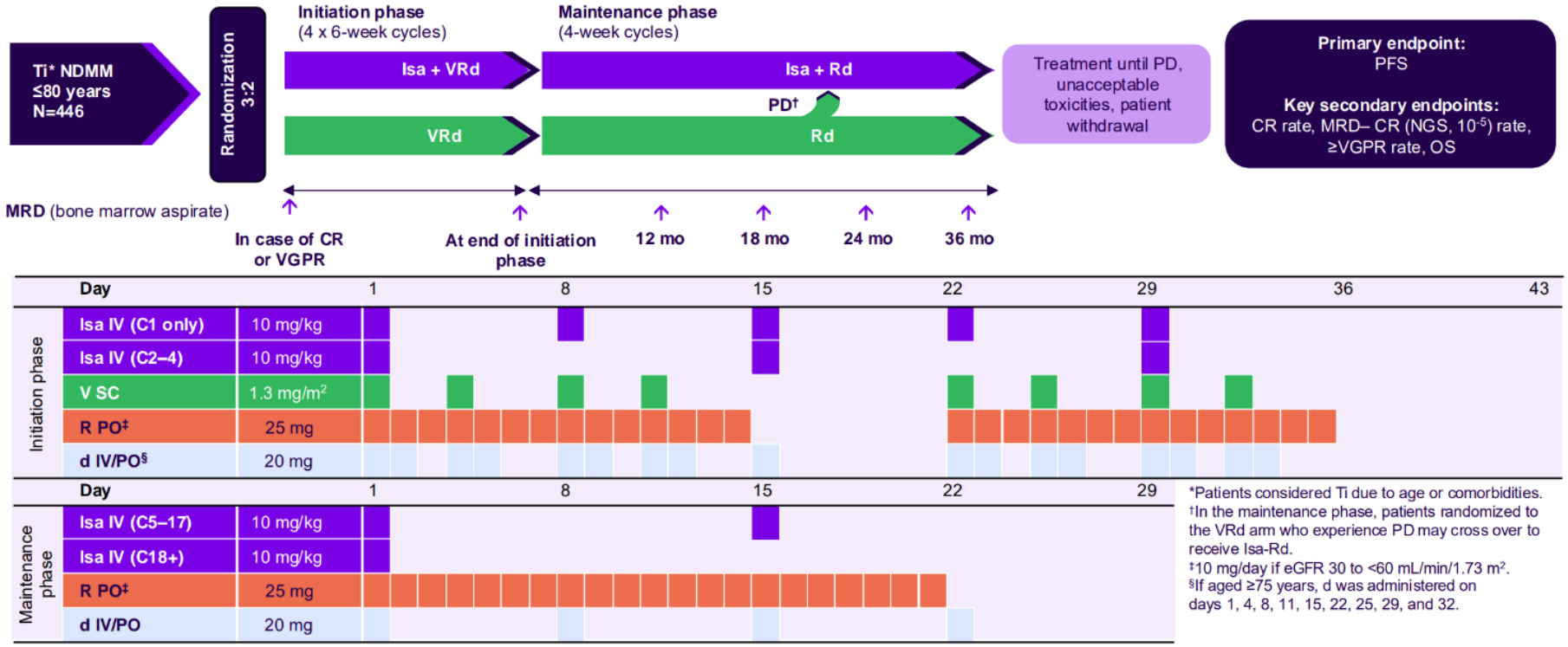
Abbreviations: HRQoL, health-related quality of life; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation, VRd, bortezomib, lenalidomide, and dexamethasone.

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

B.2.3.1 *Comparative summary of RCT methodology*

The IMROZ study was a Phase III, prospective, multicentre, international, randomised, open-label, 2-arm parallel group study to assess the clinical benefit of IsaVRd (active group) versus VRd (control group) for the treatment of participants with NDMM who are not eligible for ASCT. The trial design for IMROZ is presented in Figure 6.

Figure 6: IMROZ clinical trial design



Abbreviations: C, cycle; CR, complete response; d, dexamethasone; eGFR, estimated glomerular filtration rate; Isa, isatuximab; IV, intravenous; mo, month; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGS, next generation sequencing; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, per os; R, lenalidomide; Rd, lenalidomide and dexamethasone; SC, subcutaneous; Ti, transplant ineligible; B, bortezomib; VGPR, very good partial response; VRd, bortezomib, lenalidomide, and dexamethasone.
† Isatuximab (Isa + VRd arm only) will be given intravenously (IV) at the dose of 10 mg/kg on Days 1, 8, 15, 22, 29 in Cycle 1; from Cycle 2 onwards, it will be given on Days 1, 15, 29.
* In the continuous phase, isatuximab will be reduced to every 4 weeks after 18 cycles of treatment.
** In the continuous phase, patients randomised to the VRd arm who experience PD may crossover to receive IsaRd.

Table 8: Summary of trial methodology

Trial number (acronym)	**NCT03319667 (IMROZ)**
Location	93 sites across 21 countries
Trial design	Prospective, multicentre, international, randomised, open-label, 2-arm parallel group study. **Treatment arms** Patients were randomly assigned in a 3:2 ratio to one of two treatment arms: • Isatuximab in combination with bortezomib, lenalidomide, and dexamethasone (IsaVRd, experimental arm) • Bortezomib in combination with lenalidomide and dexamethasone (VRd, control arm) **Crossover** Patients randomised in the VRd arm were allowed to crossover from lenalidomide and dexamethasone in the continuous phase to receive isatuximab in combination with lenalidomide and dexamethasone only in case of progression. Patients who permanently discontinued lenalidomide and dexamethasone due to a related adverse event occurring less than 6 months before the crossover, consent withdrawal, or for any reason other than progressive disease, were not eligible for crossover.

Eligibility criteria for participants	**Key inclusion criteria**
	Main study
	• Adults with multiple myeloma
	• Evidence of measurable disease
	  ○ Serum M-protein ≥1.0 g/dL measured using serum protein immunoelectrophoresis and/or
	  ○ Urine M-protein ≥200 mg/24 hours measured using urine protein immunoelectrophoresis and/or
	  ○ Serum free light chain multiple myeloma without measurable disease in serum or urine
	• Patients who are newly diagnosed and not considered for high-dose chemotherapy due to:
	  ○ Age ≥65 years; or <65 years with important comorbidities likely to have a negative impact on tolerability of high dose chemotherapy with SCT
	• Patient has given voluntary written informed consent before performance of any study related procedures not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to his/her medical care
	Crossover
	• Patient with confirmed PD in the VRd control arm prior to crossover

	• Patient has not received any other systemic anticancer therapy(ies) other than the VRd arm **Key exclusion criteria** **Main study** • Less than 18 years (or country's legal age of majority if the legal age is >18 years) and more than 80 years of age • Peripheral neuropathy Grade >1 or Grade 1 with pain • Diagnosis of amyloidosis, monoclonal gammopathy of undetermined significance, or smouldering multiple myeloma • Diagnosis of Waldenström's disease, or other conditions in which IgM M-protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions • Prior or current systemic therapy or SCT for multiple myeloma, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for 4 days) of corticosteroids, if completed within 14 days prior to randomisation • Concomitant plasma cell leukaemia • Any major procedure within 14 days before the initiation of the study treatment • ECOG PS >2 • Haemoglobin <8 g/dL • Platelets <70×10^9/L if <50% of BM nucleated cells are plasma cells, and ≤30×10^9/L if ≥50% of BM nucleated cells are plasma cells. Platelet transfusion is not allowed within 3 days before the screening haematological test • Absolute neutrophil count (ANC) <1,000/µL (1×10^9/L) • Creatinine clearance <30 mL/min/1.73 m² • Total bilirubin >1.5 × upper limit of normal (ULN) • Corrected serum calcium >14 mg/dL (>3.5 mmol/L) • Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3×ULN • Hypersensitivity (or contraindication) to dexamethasone, sucrose histidine (as base and hydrochloride salt), boron, mannitol, and polysorbate 80 or any of the components of study therapy that are not amenable to premedication with steroids, or H2 blockers that would prohibit further treatment with these agents • Second/third degree heart block, poorly controlled hypertension, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, New York Heart Association class III or IV congestive heart failure, Grade ≥3 arrhythmias, or stroke or transient ischemic attack in the previous 6 months prior to randomisation • Left-ventricular ejection fraction <40% • Prior malignancy • Known AIDS-related illness or known HIV disease requiring antiviral treatment, or active hepatitis A, B, or C infection

	• Malabsorption syndrome or any condition that can significantly impact the absorption of lenalidomide • Unable or unwilling to undergo thromboprophylaxis as per local clinical practice • Any of the following within 3 months prior to randomisation: treatment resistant peptic ulcer disease, erosive esophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism, or other uncontrolled thromboembolic event • Any severe acute or chronic medical condition which could impair the ability of the patient to participate in the study or interfere with interpretation of study results • Pregnant or breastfeeding woman or woman who intends to become pregnant during the study • Male participants who disagree to practice true abstinence or disagree to use a condom during sexual contact with a pregnant woman or a woman of childbearing potential while participating in the study, during dose interruptions, and for at least 28 days following discontinuation of study lenalidomide, or for 3 months after discontinuation of bortezomib treatment, or 5 months after discontinuation of isatuximab, whichever occurs last, even if he has undergone a successful vasectomy **Crossover** • Diagnosis of amyloidosis, monoclonal gammopathy of undetermined significance, or smouldering multiple myeloma • Diagnosis of Waldenström's disease, or other conditions in which IgM M-protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions • Concomitant plasma cell leukaemia • Any major procedure within 14 days before the initiation of the study treatment: plasmapheresis, major surgery • ECOG PS >2 • Haemoglobin <8 g/dL • Platelets $<70\times10^9$/L if <50% of BM nucleated cells are plasma cells, and $\leq30\times10^9$/L if ≥50% of BM nucleated cells are plasma cells. Platelet transfusion is not allowed within 3 days before the screening haematological test • Absolute neutrophil count <1,000/µL (1×10^9/L). The use of G-CSF is not allowed to reach this level • Creatinine clearance <30 mL/min/1.73 m² • Total bilirubin >1.5×ULN except for known Gilbert syndrome • Corrected serum calcium >14 mg/dL (>3.5 mmol/L) • Aspartate aminotransferase and/or ALT >3×ULN • Hypersensitivity (or contraindication) to dexamethasone, sucrose histidine (as base and hydrochloride salt), boron, mannitol, and polysorbate 80 or any of the components of study therapy that are not amenable to premedication with steroids, or H2 blockers that would prohibit further treatment with these agents

	• Second/third degree heart block, poorly controlled hypertension, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, New York Heart Association class III or IV congestive heart failure, Grade ≥3 arrhythmias, or stroke or transient ischemic attack in the previous 6 months prior to randomisation • Left-ventricular ejection fraction <40% • Prior malignancy • Known AIDS-related illness or known HIV disease requiring antiviral treatment, or active hepatitis A, B, or C infection • Malabsorption syndrome or any condition that can significantly impact the absorption of lenalidomide • During the main study, premature discontinuation of lenalidomide and dexamethasone due to a related AE occurring less than 6 months before the start of crossover part, consent withdrawal, or for any reason other than PD • Unable or unwilling to undergo thromboprophylaxis as per local clinical practice • Any of the following within 3 months prior to randomisation: treatment resistant peptic ulcer disease, erosive esophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism, or other uncontrolled thromboembolic event • Any severe acute or chronic medical condition which could impair the ability of the patient to participate in the study or interfere with interpretation of study results • Pregnant or breastfeeding woman or woman who intends to become pregnant during the study • Male participants who disagree to practice true abstinence or disagree to use a condom during sexual contact with a pregnant woman or a woman of childbearing potential while participating in the study, during dose interruptions, and for at least 28 days following discontinuation of study lenalidomide, or for 3 months after discontinuation of bortezomib treatment, or 5 months after discontinuation of isatuximab, whichever occurs last, even if he has undergone a successful vasectomy
Trial drugs	Intervention: IsaVRd (n=265) Comparator: VRd (n=181) **Isatuximab** Intravenous isatuximab dosed at 10 mg/kg will be given as follows: • Induction period (IsaVRd arm): Days 1, 8, 15, 22, and 29 of Cycle 1 and Days 1, 15, and 29 of Cycles 2 to 4 (each cycle duration is 42 days) • Continuous treatment period (IsaVRd arm): Days 1 and 15 of each cycle (each cycle duration is 28 days). Starting with Cycle 18 of treatment (counting from the beginning of the induction period), if the patient is still on the trial, the schedule will be switched to a once every 4 weeks administration • Crossover: Days 1, 8, 15, and 22 of Cycle 1, and Days 1 and 15 in subsequent cycles **Dexamethasone** Intravenous dexamethasone at 20 mg/day will be given as follows (otherwise PO):

	• Induction period (IsaVRd and VRd arms): Days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32 and 33. If patients are ≥75 years old, dexamethasone will be administered on Days 1, 4, 8, 11, 15, 22, 25, 29, and 32 • Continuous treatment period (IsaVRd and VRd arms): Days 1, 8, 15 and 22 of each cycle. Dose modifications may be recommended based on dose toxicity • Crossover: Days 1, 8, 15 and 22 of Cycle 1 and Days 1 and, 15 in subsequent cycles **Lenalidomide** • Oral lenalidomide dosed at 25 mg/day (10 mg/day for patients with CrCl ≥30 to <60 mL/min) will be given as follows: • Induction period: from Days 1 to 14 and from Days 22 to 35 of Cycle 1 to 4 • Continuous treatment period: from Days 1 to 21. Dose modifications may be recommended based on dose toxicity • Crossover: Days 1 to 21 **Bortezomib** • Subcutaneous bortezomib dosed at 1.3 mg/m^2 will be given during the induction period on Days 1, 4, 8, 11, 22, 25, 29, and 32 of all induction cycles • Dose modifications may be recommended based on dose toxicity • Patients with a body surface area (BSA) >2.2 m² will use 2.2 m² for the determination of bortezomib dose • Bortezomib is only given during the induction period, i.e. it is not given during the continuous treatment period
Permitted and disallowed concomitant medication	**Permitted** • Viral prophylaxis: For patients receiving bortezomib, prophylaxis is required against herpes zoster using oral acyclovir, or valacyclovir, or equivalent antiviral therapy per institutional guidelines and at the discretion of the site Investigator. • Antithrombotic therapy: As lenalidomide increases the risk of venous thromboembolism, all patients should receive prophylactic antithrombotic treatment unless there is an excessive risk of bleeding (e.g. aspirin etc). • Granulocyte colony-stimulating factor (G-CSF) prophylaxis: Prophylactic administration of G-CSF may be used in patients experiencing recurrent difficulties with neutropenia. • Glucocorticoids, antihistamines, and analgesics for the management of IRs **Prohibited** • Any other anti-myeloma therapy not specified in the protocol, including immunotherapy, hormonal therapy, targeted therapy or biological therapies, other investigational drug, or curative radiotherapy. • Systemic corticosteroids • Live vaccines • Co-administration of strong inhibitors of CYP 3A4 unless benefit outweighs the risk

	• Concomitant use of strong CYP3A4 inducers is not recommended
Primary outcomes (including scoring methods and timings of assessments)	PFS defined as the time from the date of randomisation to the date of first documentation of PD [as determined by the IRC], or date of death from any cause, whichever occurred first
Other outcomes used in the economic model/specified in the scope	Secondary outcomes • Overall survival, defined as the time from the date of randomisation to death from any cause • Time to treatment discontinuation, defined as the difference between the first definitive treatment discontinuation date and the date of first exposure to treatment
Pre-planned subgroups	Subgroup analyses of PFS and TEAEs were conducted

Abbreviations: AIDS, acquired immunodeficiency syndrome; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BM, bone marrow; BSA, body surface area; CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte colony-stimulating factor; HIV, human immunodeficiency virus; IR, infusion reaction; IRC, independent review committee; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; PD, progressive disease; PFS, progression-free survival; PO, per os; PS, performance status; SCT, stem cell transplantation; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; VRd, bortezomib, lenalidomide, and dexamethasone.

B.2.3.1.1 Patient Disposition

In total, 512 participants were screened, and 446 participants were randomised across 93 sites in 21 countries; the countries with the largest enrolment included France (n=78), Czechia (n=52), Turkey (n=47), Australia (n=41), and Greece (n=32). No patients were from the UK. Of the patients enrolled in the trial, 181 participants were randomised to VRd, and 265 participants were randomised to IsaVRd; two patients in the IsaVRd group did not receive treatment (Table 9).

At the time of the data cut-off for PFS analysis (26 September 2023), 275 participants had discontinued study intervention (138 [52.1%] in the IsaVRd group and 137 [75.7%] in the VRd group) (Table 9).

Table 9: Patient disposition

	IsaVRd n (%) (N=265)	**VRd n (%) (N=181)**
Randomised and not treated	2 (0.8)	0
Randomised and treated	263 (99.2)	181 (100)
Patients still on treatment	125 (47.2)	44 (24.3)
Patients with definitive treatment discontinuation	138 (52.1)	137 (75.7)
Reason for definitive treatment discontinuation		
Adverse event	60 (22.6)	50 (27.6)
Related to COVID-19	8 (3.0)	4 (2.2)
Progressive disease	38 (14.3)	67 (37.0)
Poor compliance to protocol	6 (2.3)	0
Withdrawal by subject	23 (8.7)	16 (8.8)
Other	11 (4.2)	4 (2.2)
Related to COVID-19	1 (0.4)	0
Reason for treatment withdrawal by subject		
Adverse event	9 (3.4)	5 (2.8)
Related to COVID-19	1 (0.4)	0
Study procedure	1 (0.4)	1 (0.6)
Other	13 (4.9)	10 (5.5)
Related to COVID-19	2 (0.8)	0
Patients still on study	178 (67.2)	109 (60.2)
Patients who ended the study	87 (32.8)	72 (39.8)
Reason for end of study		
Completed	0	0
Death	69 (26.0)	59 (32.6)
Poor compliance to protocol	0	0
Withdrawal by subject	14 (5.3)	12 (6.6)

	IsaVRd n (%) (N=265)	VRd n (%) (N=181)
Other	4 (1.5)	1 (0.6)
Status at the cut-off date†		
Alive	196 (74.0)	122 (67.4)
Death	69 (26.0)	59 (32.6)
Time from last contact to the cut-off date‡		
≤2 weeks	11 (4.2)	6 (3.3)
>2 weeks and ≤1 month	2 (0.8)	1 (0.6)
>1 month and ≤2 months	0	0
>2 months and ≤3 months	0	1 90.6)
>3 months	18 (6.8)	15 (8.3)

Abbreviations: CSR, clinical study report; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone combination; VRd, bortezomib, lenalidomide, and dexamethasone combination.
† Cut-off date for overall survival (26 September 2023).
‡ For patients censored for overall survival before the cut-off date.
Note: Definitive treatment discontinuation is defined as the discontinuation of all the study drugs. When all study drugs are not discontinued at the same time, the reason for definitive discontinuation is the reason for discontinuation of the last study drug stopped.
Note: Percentages are calculated using the number of patients randomised as denominator.
Source: IMROZ CSR, 2024 (88).

B.2.3.1.2 Patient demographics and background characteristics

Baseline patient demographics are provided in Table 10. In total, 237 (53.1%) participants were male. A total of 323 (72.4%) participants were white and 48 (10.8%) were Asian; for 64 (14.3%) participants, the race was not reported/missing. Overall, participants had a median age of 72.0 years (range: 55.0 to 80.0 years); 126 of the 446 participants (28.3%) were aged 75 years or older. Most participants were in Europe (275 [61.7%]).

Table 10: Demographic characteristics

	IsaVRd (N=265)	VRd (N=181)	All (N=446)
Age (years)			
Mean (SD)	71.7 (4.0)	71.5 (4.8)	71.6 (4.4)
Median	72.0	72.0	72.0
Q1; Q3	69.0; 75.0	68.0; 75.0	69.0; 75.0
Min; Max	60; 80	55; 80	55; 80
Age group (years) [n (%)]			
<65	8 (3.0)	9 (5.0)	17 (3.8)
65–69‡	73 (27.5)	47 (26.0)	120 (26.9)
70–74‡	115 (43.4)	68 (37.6)	183 (41.0)
75–80‡	69 (26.0)	57 (31.5)	126 (28.3)

	IsaVRd (N=265)	VRd (N=181)	All (N=446)
Age group 2 (years) [n (%)]			
<70	81 (30.6)	56 (30.9)	137 (30.7)
>70	184 (69.4)	125 (69.1)	309 (69.3)
Sex [n (%)]			
Female	122 (46.0)	87 (48.1)	209 (46.9)
Male	143 (54.0)	94 (51.9)	237 (53.1)
Race [n (%)]			
American Indian or Alaska Native	4 (1.5)	1 (0.6)	5 (1.1)
Asian	31 (11.7)	17 (9.4)	48 (10.8)
Black or African American	2 (0.8)	2 (1.1)	4 (0.9)
Native Hawaiian or other Pacific Island	1 (0.4)	1 (0.6)	2 (0.4)
White	192 (72.5)	131 (72.4)	323 (72.4)
Not reported/Missing	35 (13.2)	29 (16.0)	64 (14.3)
Geographical region [n (%)]			
Europe	169 (63.8)	106 (58.6)	275 (61.7)
North America	3 (1.1)	5 (2.8)	8 (1.8)
Asia	31 (11.7)	15 (8.3)	46 (10.3)
Other Countries†	62 (23.4)	55 (30.4)	117 (26.2)

Abbreviations: CSR, clinical study report; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; SD, standard deviation; VRd, bortezomib, lenalidomide, and dexamethasone.
† Other countries include Australia, New Zealand, Mexico, The Russian Federation, and Turkey.
‡ Sourced from Facon et al., 2024 (76).
Source: IMROZ CSR, 2024 (88).

B.2.3.1.3 Baseline disease characteristics

Overall, participants were well balanced between arms (less than or equal to 10% difference between arms) for disease characteristics at baseline. The median time from initial diagnosis of MM to randomisation was 1.18 months. The MM subtype at study entry was most frequently immunoglobulin G (IgG) for 286 (64.1%) participants, immunoglobulin A (IgA) for 98 (22.0%) participants, and light chain only (kappa or lambda) for 53 (11.9%) participants. There were 6 (1.3%) participants with biclonal status at study entry. The ISS stage at study entry was Stage II for 187 (41.9%) participants, Stage I for 137 (30.7%) participants, and Stage III for 120 (26.9%) participants. The R-ISS stage at study entry was most frequently Stage II for 286 (64.1%) participants, Stage I for 101 (22.6%) participants, and Stage III for 44 (9.9%) participants (Table 11).

Table 11: Disease characteristics at study entry

	IsaVRd (N=265)	VRd (N=181)	All (N=446)
Time from initial diagnosis of MM to randomisation (months)			
Mean (SD)	2.03 (3.74)	1.82 (3.27)	1.94 (3.56)

	IsaVRd (N=265)	VRd (N=181)	All (N=446)
Median	1.22	1.18	1.18
Q1; Q3	0.79; 2.10	0.79; 1.81	0.79; 1.97
Min; Max	0.3; 48.9	0.3; 37.7	0.3; 48.9
MM subtype at study entry† [n (%)]			
Ig G	171 (64.5)	115 (63.5)	286 (64.1)
Ig A	57 (21.5)	41 (22.7)	98 (22.0)
Ig M	1 (0.4)	1 (0.6)	2 (0.4)
Ig D	3 (1.1)	2 (1.1)	5 (1.1)
Ig E	0	0	0
Kappa light chain only	21 (7.9)	11 (6.1)	32 (7.2)
Lambda light chain only	11 (4.2)	10 (5.5)	21 (4.7)
Unknown/undetected	1 (0.4)	1 (0.6)	2 (0.4)
ECOG performance-status score [n (%)]‡			
0 or 1	235 (88.7)	163 (89.5)	398 (89.2)
>1	30 (11.3)	19 (10.5)	49 (11.0)
Estimated GFR <60 ml/min/1.73 m^2 [n (%)]‡	18 (6.8)	6 (3.3)	24 (5.3)
ISS stage at study entry [n (%)]			
Stage I	90 (34.0)	47 (26.0)	137 (30.7)
Stage II	107 (40.4)	80 (44.2)	187 (41.9)
Stage III	67 (25.3)	53 (29.3)	120 (26.9)
Unknown	1 (0.4)	1 (0.6)	2 (0.4)
R-ISS stage at study entry [n (%)]			
Stage I	66 (24.9)	35 (19.3)	101 (22.6)
Stage II	163 (61.5)	123 (68.0)	286 (64.1)
Stage III	27 (10.2)	17 (9.4)	44 (9.9)
Not classified	9 (3.4)	6 (3.3)	15 (3.4)
FISH assessment done but risk not classified	8 (88.9)	4 (66.7)	12 (80.0)
FISH assessment missing	0	1 (16.7)	1 (6.7)
At least one biological assessment missing	2 (22.2)	1 (16.7)	3 (20.0)
Cytogenetic risk at baseline [n (%)]‡			
Standard	207 (78.1)	140 (77.3)	347 (77.8)
High	40 (15.1)	34 (18.8)	74 (16.6)
Unknown or missing data	18 (6.8)	7 (3.9)	25 (5.6)

	IsaVRd (N=265)	VRd (N=181)	All (N=446)
High-risk chromosomal abnormalities and 1q21+ [n (%)]‡	19 (7.2)	15 (8.3)	34 (7.6)
Chromosomal abnormality [n (%)]‡			
1q21+	95 (35.8)	70 (38.7)	165 (3.7)
Amplification 1q21	32 (12.1)	23 (12.7)	55 (12.3)
Del(17p) with a 50% cutoff	15 (5.7)	9 (5.0)	24 (5.4)

Abbreviations: CSR, clinical study report; eCRF, electronic case report form; FISH, fluorescence in situ hybridisation; Ig, immunoglobulin; ISS, International Staging System; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone combination; LDH, lactate dehydrogenase; MM, multiple myeloma; Q, quarter; R-ISS, Revised International Staging System; SD, standard deviation; ULN, upper limit of normal; VRd, bortezomib, lenalidomide, and dexamethasone combination.
† As per eCRF.
‡ Sourced from Facon et al., 2024 (76).
Source: IMROZ CSR, 2024 (88).

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

B.2.4.1 *Populations analysed*

B.2.4.1.1 IMROZ

The definitions of the populations analysed in IMROZ are listed below:

- **Intent-to-treat (ITT) population**: This population included all randomised patients. Patients were analysed according to the treatment group allocated by the interactive response technology [IRT], regardless of whether patients received any study drug or received a different study drug from which they were randomised. This is the primary population for all efficacy parameters
- **Safety population**: This included patients from the ITT population who actually received at least one dose or part of a dose of the study treatments. This is the primary population for the analysis of safety parameters. This is also used for the analysis of pre-crossover exposure and safety data for crossover patients who received VRd
- **Crossover population**: This population included all patients from the VRd arm who crossed over and received at least one dose of isatuximab in the continuous phase. This population will be used for exploratory analysis of best overall response (BOR), exposure and safety data after the crossover date

B.2.4.2 *Statistical information*

A summary of the statistical methods used in the IMROZ trial is presented in Table 12.

Table 12: Summary of statistical analyses in IMROZ

Trial number (acronym)	NCT03319667 (IMROZ)
Hypothesis objective	To demonstrate the benefit of isatuximab in combination with bortezomib, lenalidomide, and dexamethasone in the prolongation of progression-free survival (PFS) as compared with bortezomib, lenalidomide, and dexamethasone in participants with newly diagnosed multiple myeloma (NDMM) not eligible for transplant
Statistical analysis	Primary analysis consisted of PFS comparison between IsaVRd and VRd arms through a log-rank test procedure stratified by the stratification factors (age and R-ISS) as entered in the IRT. The significance levels at the interim and final analyses were determined using alpha-spending to control the overall one-sided type 1 error at 2.5%. Based on the planned number of events, the one-sided nominal significance level to declare overwhelming efficacy at respectively 60% information fraction (IF) (133 PFS events), 75% IF (167 events) and 85% IF (189 events) are 0.003782, 0.008620 and 0.012036 (corresponding to HRs of 0.623, 0.686 and 0.715). The one-sided nominal significance level to declare superiority of IsaVRd at the final analysis (222 events) is 0.019937 (corresponding to a HR of 0.755). The actual alpha spending was based on the actual number of events included in the analyses and determined by the O'Brien-Fleming spending function at the time of interim and final analyses. The following estimates were provided: • The hazard ratio and corresponding two-sided confidence interval (CI) at (1-2α) % level (α being the one-sided nominal significance level at each analysis: e.g., α=0.003782 at the first PFS interim analysis if 133 events are observed) will be estimated using the Cox proportional hazards model stratified by the same stratification factors as those used for the log-rank test described above. Underlying assumptions of the Cox Proportional hazards model will be assessed by graphical methods (i.e., log-log graphical methods) • PFS data was analysed using the Kaplan-Meier method by treatment group in the ITT population ○ Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and their associated two-sided 95% CIs were provided. The 95% confidence intervals were constructed using a log-log transformation of the survival function and the methods of Brookmeyer and Crowley
Sample size, power calculation	The sample size calculation was based on the primary efficacy endpoint of PFS using the following assumptions: • Progression-free survival has an exponential distribution in both treatment arms • The VRd arm will have a median PFS of 40 months • The IsaVRd arm will have 36% risk reduction in hazard rate in comparison to VRd arm. The targeted HR is 0.64, which corresponds to an improvement in the true median PFS time from 40.0 months to 62.5 months • A stratified log-rank test at an overall 1-sided 2.5% significance level with 90% power • An interim analysis for efficacy assessment on PFS is planned when 60% of the PFS events will be observed. An O'Brien and Fleming α-spending function will be used to obtain the nominal significance levels for the interim and final analyses of PFS • A randomisation ratio of 3:2 (IsaVRd:VRd)

Trial number (acronym)	NCT03319667 (IMROZ)
	Based on the above assumptions, a total of 222 PFS events are needed to achieve a 90% power for the study. In total, 440 patients (264 in IsaVRd arm and 176 in the VRd arm) would be adequate in the global study part to achieve the targeted number of events for PFS. Assuming a uniform accrual rate of 30 patients per month, the final analysis cut-off date of PFS will be approximately 60 months after first patient in (FPI). With the addition of one interim analysis when 75% of the PFS events will be observed, the power will be decreased from 90.1% to 89.7 %. With the addition of a third interim analysis when 85% of PFS events will be observed, the power will be decreased to 89.4%.
Data management	Study centres were visited at regular intervals based on RBM process and a Visit Log was maintained. Monitors were responsible for reviewing adherence to the protocol, compliance with GCP, and the completeness, accuracy, and consistency of the data. Case report form data were captured via data entry by study centre personnel or the CRO in a database system owned by Medidata. Data quality checks were applied using electronic verification methods. An audit trail to support data query resolution and any modification to the data was maintained. Clinical quality assurance audits of this study were included as part of the independent Sponsor quality assessment performed by the Sponsor.
Handling of missing data	The analyses and summaries of continuous and categorical variables were based on observed data only. Percentages were calculated using as denominator the number of patients with non-missing observation in the considered population. When relevant, the number of patients with missing data is presented.

Abbreviations: CI, confidence interval; CRO, contract research organisation; FPI, first person in; GCP, good clinical practice; HR, hazard ratio; IF, information fraction; IRT, interactive response technology; ITT, intent-to-treat; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; RBM, results-based management; RCT, randomised controlled trial; R-ISS, revised international staging system; VRd, bortezomib, lenalidomide, and dexamethasone.

B.2.4.3 *Observation period*

B.2.4.3.1 IMROZ

The observation period starts from the time when the patient gives informed consent and is divided into four periods:

- The **screening period** (used equivalently as pre-treatment period in the document) is defined as the time from the signed informed consent date until the first dose of study treatments administration
- The **treatment period** is defined as the time from the first dose of study treatments administration up to the last dose of study treatments +30 days. For patients in the VRd arm who crossed over, the treatment period is the period from the date of the first dose of study treatments until the date of last dose of study

treatment before the cross over +30 days, or the crossover date –1 day, whichever is earlier

- The **crossover treatment period** is the period from first dose of isatuximab administration after crossover up to 30 days after the last dose of cross over study treatments
- The **post-treatment period** is defined as the period of time starting after the end of the treatment period date +1 day up to the end of the study, excluding the crossover treatment period (if applicable)

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

Quality assessment results for the IMROZ study are provided in Table 13.

Table 13: Quality assessment results for IMROZ

	IMROZ
Was randomisation carried out appropriately?	Yes. Study participants were randomised using an IRT in a 2:3 ratio of VRd to IsaVRd. Randomisation was stratified by country (Non-China versus China), age (<70 years vs ≥70 years) and R-ISS I or II versus III versus not classified.
Was the concealment of treatment allocation adequate?	During the trial, administration of isatuximab was open-label; no attempts were made to blind administration. The trial was open-label on ethical grounds to prevent subjecting patients in the VRd arm to unnecessary IV infusions with placebo. However, an IRT was used to prevent the investigator's knowing the treatment assignment in advance. The randomisation was the best method to avoid bias.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Overall participants were well balanced between arms (less than or equal to 10% difference between arms) for disease characteristics at baseline.
Were the care providers, participants and outcome assessors blind to treatment allocation?	No, as the administration of isatuximab was open-label, no attempt was made to blind administration. However, an IRT was used to prevent the investigator's knowing the treatment assignment in advance. The randomisation was the best method to avoid bias.
Were there any unexpected imbalances in drop-outs between groups?	No, discontinuation rates were similar across the two treatment groups. Overall, 47 (26.0%) and 60 (22.8%) participants in the VRd and IsaVRd groups, respectively, had TEAEs leading to definitive treatment discontinuation.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All outcomes were related to the clinical goals of isatuximab therapy. Additionally, the primary and key secondary outcomes listed in the methodology section are consistent with those reported in the results section.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate	Yes. The ITT population included all patients who gave their informed consent and had a randomisation number confirmed by the IRT. This population was the

	IMROZ
methods used to account for missing data?	primary population for efficacy analyses and all analyses using this population were based on the treatment assigned at randomisation. The analyses and summaries of continuous and categorical variables were based on observed data only. Percentages were calculated using the number of patients with non-missing observation in the considered population as the denominator. When relevant, the number of patients with missing data is presented.

Abbreviations: IRT, interactive response technology; ITT, intent-to-treat; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; R-ISS, revised international staging system; TEAE, treatment-emergent adverse event; VRd, bortezomib, lenalidomide, and dexamethasone.

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

B.2.6.1 *Study IMROZ*

B.2.6.1.1 Primary efficacy outcome

Progression-free survival

The primary endpoint was PFS, which was defined as the time from the date of randomisation to the date of first documentation of progressive disease (PD) (as determined by the IRC), or the date of death from any cause, whichever occurred first.

In the ITT population, as of the cut-off date of 26 September 2023, 84 (31.7%) and 78 (43.1%) patients experienced death or disease progression in the IsaVRd and VRd groups, respectively, and the median follow-up was 59.73 months (Table 14). The HR was 0.596 (98.5% CI; 0.406,0.876; p=0.0005), corresponding to a 40.4% reduction in the risk of disease progression or death with IsaVRd compared with VRd. The median PFS was not reached (NR) in the IsaVRd group and was 54.34 months (95% CI; 45.207, NR) in the VRd group. For VRd, both the observed HR (0.596) and the median PFS (54.34 months) exceeded the study hypothesis (0.64 and 40 months, respectively). An early separation between the VRd and IsaVRd groups was observed in the PFS curve (Figure 7). At 60 months, the PFS probability was 63.2% in the IsaVRd group and 45.2% in the VRd group.

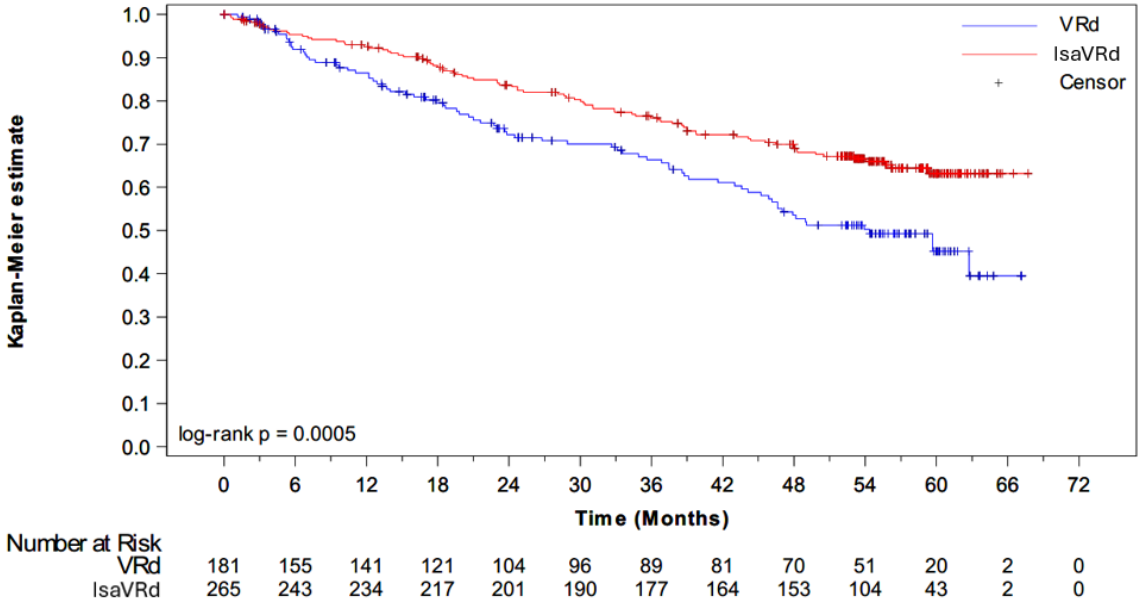
Table 14: PFS – Primary analysis based on disease assessment by the IRC by treatment group – ITT population

	IsaVRd (N=265)	**VRd (N=181)**
Number (%) of events	84 (31.7)	78 (43.1)
Number (%) of patients censored	181 (68.3)	103 (56.9)
Median (95% CI)	NR (NR, NR)	54.34 (45.207, NR)
Stratified† hazard ratio vs VRd (98.5154% CI)	0.596 (0.406, 0.876)	
Stratified† Log-Rank test p-value	0.0005	
PFS probability (95% CI)		
6 Months	0.953 (0.920, 0.973)	0.919 (0.867, 0.951)
12 Months	0.926 (0.886, 0.952)	0.864 (0.803, 0.908)
18 Months	0.882 (0.835, 0.916)	0.796 (0.726, 0.850)
24 Months	0.837 (0.785, 0.877)	0.722 (0.646, 0.785)
30 Months	0.803 (0.748, 0.847)	0.701 (0.622, 0.766)
36 Months	0.761 (0.702, 0.809)	0.664 (0.583, 0.732)
42 Months	0.722 (0.661, 0.774)	0.611 (0.528, 0.684)
48 Months	0.699 (0.637, 0.753)	0.535 (0.451, 0.613)
54 Months	0.666 (0.602, 0.723)	0.503 (0.417, 0.582)

	IsaVRd (N=265)	VRd (N=181)
60 Months	0.632 (0.562, 0.694)	0.452 (0.356, 0.542)
66 Months	0.632 (0.562, 0.694)	0.395 (0.264, 0.523)

Abbreviations: CI, confidence interval; CSR, clinical study report; IRC, Independent Response Committee; ITT, intent-to-treat; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; NR, not reached; PFS, progression-free survival; VRd, bortezomib, lenalidomide, and dexamethasone.
Cut-off date: 26 September 2023. Median follow-up time = 59.73 months.
Note: Events occurring more than 13 weeks after the last valid disease assessment are censored.
If progression or death was not observed before the PFS analysis cut-off date or the date of initiation of further anti-myeloma treatment, PFS was censored at the date of the last valid disease assessment with no evidence of a disease progression performed prior to initiation of a further anti-myeloma treatment (if any) or the PFS analysis cut-off date, whichever occurred first.
Source: IMROZ CSR, 2024 (88).

Figure 7: PFS – Primary analysis based on disease assessment by the IRC – Kaplan-Meier curves by treatment group – ITT population



Abbreviations: CSR, clinical study report; IRC, Independent Response Committee; IRT, Interactive Response Technology; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; ITT, intent-to-treat; PFS, progression-free survival; R-ISS, Revised International Staging System; VRd, bortezomib, lenalidomide, and dexamethasone.

Source: IMROZ CSR, 2024 (88).

At the time of the cut-off date, a total of 181 (68.3%) and 103 (56.9%) participants in the IsaVRd and VRd groups, respectively, did not have a PFS event and were censored. The main reason for censoring was end of trial follow-up (34.7% and 35.4% in the IsaVRd and VRd groups, respectively). Overall, 84 (31.7%) and 78 (43.1%) participants had an event in the IsaVRd and VRd groups, respectively. Among study participants with events, disease progression was reported in 50 (59.5%) and 66 (84.6%) patients in the IsaVRd and VRd groups, respectively. Death without disease progression was reported in 34 (40.5%) participants in the IsaVRd group and 12 (15.4%) in the VRd group.

PFS sensitivity analyses

In sensitivity analyses of PFS, a benefit was apparent in most subgroups. For further information on PFS sensitivity analyses, refer to Appendix M.1.

PFS multivariate analysis

For results for the PFS multivariate analysis, refer to Appendix M.2.

PFS by next generation sequencing (NGS) MRD status

For results for the PFS by NGS MRD status, refer to Appendix M.3.

B.2.6.1.2 Secondary efficacy outcomes

Summary of secondary endpoints

A summary of the overall response rates and main secondary endpoints is provided in Table 15. Detailed information on all secondary endpoints is included in Appendix M.4.

Table 15: Summary of overall response rate as per IRC and main secondary endpoints – ITT population

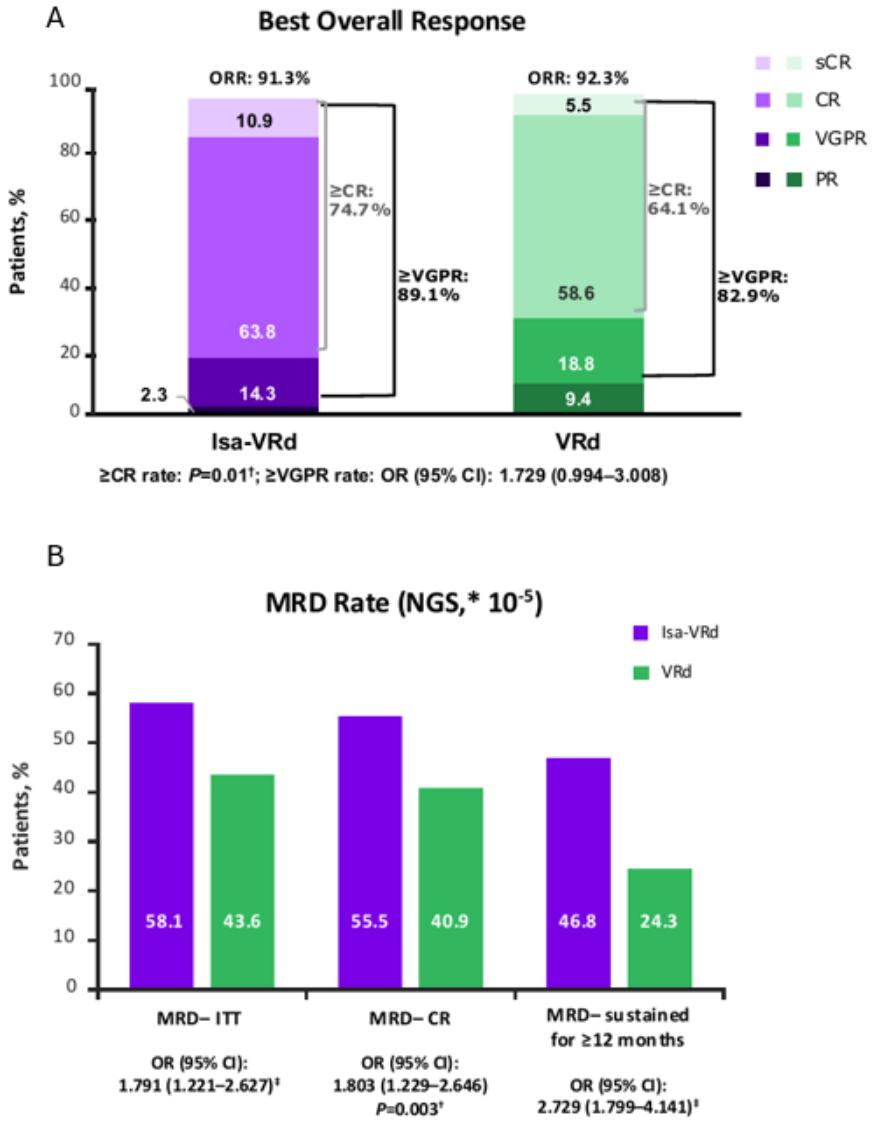
	IsaVRd (N=265)	**VRd (N=181)**
Best Overall Response [n (%)]		
Stringent complete response	29 (10.9)	10 (5.5)
Complete response	169 (63.8)	106 (58.6)
Very good partial response	38 (14.3)	34 (18.8)
Biochemical CR but with missing bone marrow	2 (0.8)	8 (4.4)
Near-CR	23 (8.7)	7 (3.9)
Partial response	6 (2.3)	17 (9.4)
Minimal response	0	0
Stable disease	18 (6.8)	11 (6.1)
Non-Progressive disease	0	0
Progressive disease	0	1 (0.6)
Unconfirmed progressive disease	0	0
Not evaluable/Not assessed	5 (1.9)	2 (1.1)
Overall response [% (95% CI)]		
Responders (sCR, CR, VGPR or PR)	91.3 (87.26, 94.42)	92.3 (87.36, 95.71)
Stratified Odds ratio (95% CI) vs VRd	0.888 (0.439 to 1.794)	
Stratified Cochran-Mantel-Haenszel test p-value vs VRd	0.6295	
Complete response (sCR or CR) [% (95% CI)]	74.7 (69.04, 79.84)	64.1 (56.64, 71.07)
Stratified Odds ratio (95% CI) vs VRd	1.656 (1.097, 2.500)	

	IsaVRd (N=265)	VRd (N=181)
Stratified Cochran-Mantel-Haenszel test p-value vs VRd	0.0080*	
NGS MRD[−] CR rate [% (95% CI)]	55.5 (49.27, 61.55)	40.9 (33.65, 48.42)
Stratified Odds ratio (95% CI) vs VRd	1.803 (1.229, 2.646)	
Stratified Cochran-Mantel-Haenszel test p-value vs VRd	0.0013*	
VGPR or better [% (95% CI)]	89.1 (84.66, 92.55)	82.9 (76.58, 88.06)
Stratified Odds ratio (95% CI) vs VRd	1.729 (0.994, 3.008)	
Stratified Cochran-Mantel-Haenszel test p-value vs VRd	0.0259	
NGS MRD negativity rate (NGS, 10^{-5}) [% (95% CI)]	58.1 (51.92, 64.12)	43.6 (36.30, 51.20)
Stratified Odds ratio (95% CI) vs VRd	1.791 (1.221, 2.627)	
Stratified Cochran-Mantel-Haenszel test p-value vs VRd	0.0014	
NGS Sustained MRD negativity ≥12 months rate [% (95% CI)]	46.8 (40.66, 53.00)	24.3 (18.25, 31.23)
Stratified Odds ratio (95% CI) vs VRd	2.729 (1.799, 4.141)	
Stratified Cochran-Mantel-Haenszel test p-value vs VRd	<0.0001	

Abbreviations: CI, confidence interval; CR, complete response; CSR, clinical study report; IRC, Independent Response Committee; ITT, intent-to-treat; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; MRD, minimal residual disease; NGS, next-generation sequencing; PR, partial response; sCR, stringent complete response; VGPR, very good partial response; VRd, bortezomib, lenalidomide, and dexamethasone.
Source: IMROZ CSR, 2024 (88).

IsaVRd followed by IsaRd resulted in deep response rates, with a significant improvement in the MRD- CR rate, as well as higher rates of MRD- and sustained MRD- for ≥12 months. The time to MRD- (median [95% CI]) was 14.72 (11.53, 24.08) months for IsaVRd and 32.79 (17.51, 45.11) months for VRd (Figure 8).

Figure 8: Depth of response



Abbreviations: CI, confidence interval; CR, complete response; Isa-VRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; ITT, intent-to-treat; MRD, minimal residual disease; NGS, next generation sequencing; OR, overall response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response; VRd, bortezomib, lenalidomide, and dexamethasone.

Overall survival

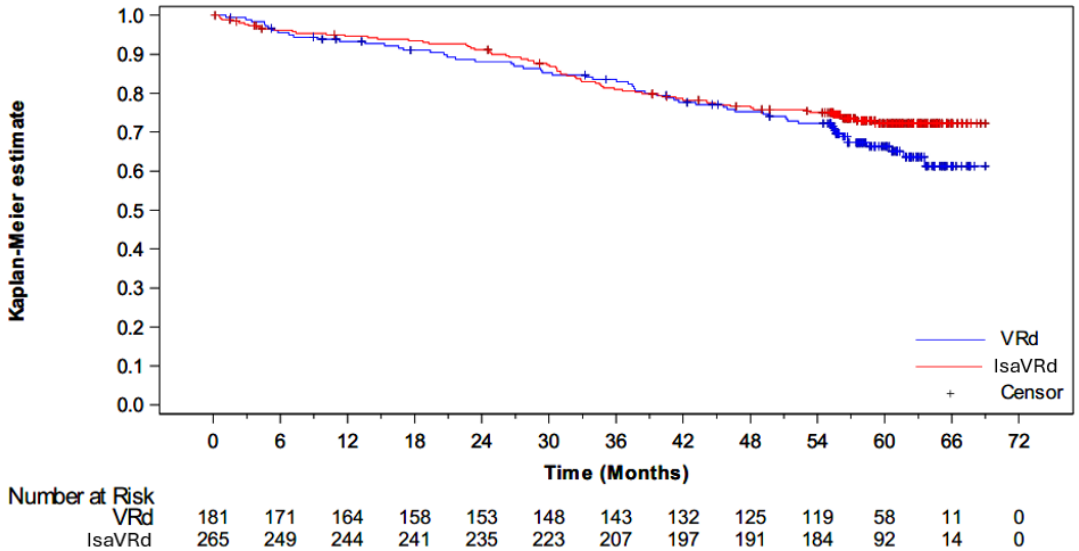
An interim analysis of OS for futility and overwhelming efficacy was planned at the time of the interim analysis of PFS. At a median follow-up of 59.73 months at the cut-off date of 26 September 2023, 69 (26.0%) and 59 (32.6%) participants had a death event in the IsaVRd and VRd groups, respectively (Table 16). The HR for OS for IsaVRd vs VRd was 0.776 (99.97% CI; 0.407, 1.480), which passed the pre-specified futility threshold (that was set to HR above 1.1). The one-sided nominal p-value was 0.076. Median OS was not reached in either group (Figure 9).

Table 16: Overall survival by treatment group – ITT population

	IsaVRd (N=265)	VRd (N=181)
Number (%) of deaths	69 (26.0)	59 (32.6)
Number (%) of patients censored	196 (74.0)	122 (67.4)
Median (95% CI)	NR	NR
Stratified† Hazard ratio (99.9725% CI) vs VRd	0.776 (0.407 to 1.48)	
Stratified Log-Rank test p-value vs VRd	0.0760	
Survival probability (95% CI)		
6 Months	0.962 (0.930, 0.979)	0.956 (0.913, 0.978)
12 Months	0.946 (0.911, 0.968)	0.933 (0.885, 0.961)
18 Months	0.935 (0.897, 0.959)	0.910 (0.857, 0.944)
24 Months	0.911 (0.870, 0.940)	0.881 (0.824, 0.921)
30 Months	0.872 (0.825, 0.908)	0.853 (0.791, 0.897)
36 Months	0.810 (0.756, 0.853)	0.835 (0.772, 0.882)
42 Months	0.782 (0.727, 0.828)	0.777 (0.707, 0.832)
48 Months	0.766 (0.710, 0.813)	0.753 (0.681, 0.810)
54 Months	0.750 (0.692, 0.799)	0.722 (0.649, 0.783)
60 Months	0.723 (0.661, 0.775)	0.663 (0.585, 0.731)
66 Months	0.723 (0.661, 0.775)	0.613 (0.518, 0.695)

Abbreviations: CI, confidence interval; CSR, clinical study report; ITT, intent-to-treat; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; NR, not reached; VRd, bortezomib, lenalidomide, and dexamethasone.
Cut-off date: 26 September 2023. Median follow-up time = 59.73 months. Source: IMROZ CSR, 2024 (88).

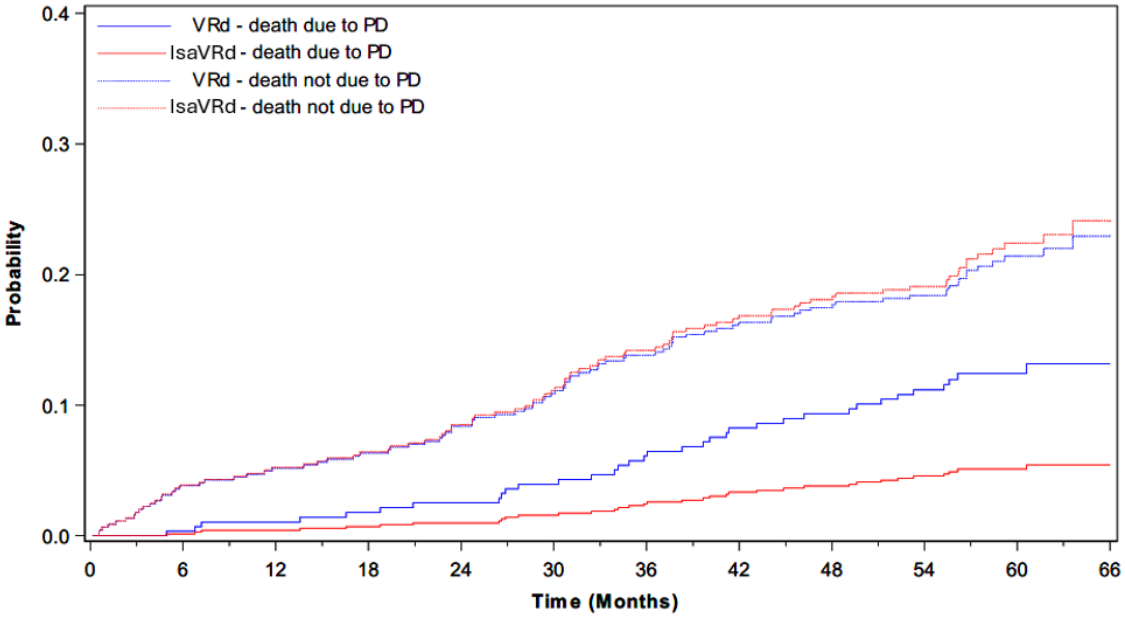
Figure 9: Overall survival – Kaplan-Meier curves by treatment group – ITT population



Abbreviations: CSR, clinical study report; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; ITT, intent-to-treat; VRd, bortezomib, lenalidomide, and dexamethasone.
Cut-off date: 26 September 2023.
Source: IMROZ CSR, 2024 (88).

It should be noted that the difference in observed death events (26% on IsaVRd and 32.6% on VRd) was largely due to a difference in disease progression (4.9% on IsaVRd and 12.2% on VRd). This was supported by a further analysis of time to death by cause of death. This analysis indicated that the positive survival trend in favour of the IsaVRd arm was due to the lower mortality due to disease progression (HR: 0.394 [95% CI; 0.199, 0.783]) with early separation of the curves. There was no difference in time to death due to causes other than myeloma progression (HR: 1.012; [95% CI; 0.668, 1.533]) (Figure 10).

Figure 10: Time to death based on cause-specific analysis: cumulative incidence function curves - ITT population



Abbreviations: CSR, clinical study report; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; ITT, intent-to-treat; PD, progressive disease; VRd, bortezomib, lenalidomide, and dexamethasone.
Cut-off date: 26 September 2023.
Source: IMROZ CSR, 2024 (88).

B.2.6.1.3 Adjusting for Treatment crossover and subsequent therapies

In addition to treatment crossover specified in the study protocol, IMROZ also included several subsequent treatments not routinely available in NHS clinical practice.

To meet requirements of HTA submission, NICE DSU 16 (91) and 24 (92) were used to inform survival analyses that adjusted for crossover from Rd to isatuximab, lenalidomide, and dexamethasone (IsaRd) in the continuous treatment phase (which would not be routine practice in the UK), with and without adjustment for subsequent anti-cancer therapies not used in clinical practice in the UK.

Below we report the post-hoc OS adjustment analysis for combined crossover and treatments not available in NHS clinical practice as this reflects outcomes expected in routine practice.

Patients included in treatment cross-over adjustment

In the IsaVRd arm, 52/265 (19.6%) patients received at least one further anti-cancer therapy compared with 80/181 (44.2%) patients in the VRd arm (Table 17). Of those, 25/181 (13.8%) patients crossed over from VRd to IsaRd in the continuous phase for patients receiving VRd induction therapy (control arm), which could not occur in the IsaVRd arm. Of the patients who had at least one further anti-cancer therapy in the VRd arm, 45 out of 80 (56.2%) received a subsequent treatment not used in NHS clinical practice. This includes the 25 patients who crossed over from Rd to IsaRd, as their crossover treatment is not available in NHS practice.

Table 17: Summary of patients who received further anti-cancer therapy

	IsaVRd (N=265)	VRd (N=181)
At least one further anti-cancer therapy, n (%)	52 (19.6)	80 (44.2)
Cross-over to IsaRd	–	25 (13.8)
Other anti-cancer therapy	52 (19.6)	55 (30.4)
Total patients adjusted for a treatment not available in the NHS clinical practice	25 (9.4)	45 (24.9)

Abbreviations: IsaRd, isatuximab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; NHS, National Health Service; VRd, bortezomib, lenalidomide, and dexamethasone.

In total, 71 different regimens, including crossover to IsaRd, were used across second, third, and fourth lines by patients from IMROZ. Twenty-nine of these regimens (29/71; 40.8%) were not used in clinical practice in the UK. Moreover, 4/71 (5.6%) subsequent treatment regimens containing an anti-CD38 after IsaVRd were identified and were also adjusted for. The complete list can be found in Appendix O.2.1. To identify treatments used in NHS clinical practice, treatments were compared with regimens appraised by NICE and data from the SACT database which captured those regimens observed in a real-world setting (93).

The preferred approach for treatment switching analysis was the inverse probability of censoring weighted (IPCW) method. The choice of the method is further described in Appendix O.2.1. IPCW is a statistical technique that can adjust treatment effect estimates in the presence of informative censoring, which occurs when patients stop participating in a study for reasons related to the outcome being measured (94). By using this method, patients who switch to non-allowed treatments are artificially censored at the time of the switch. In this case, patients are artificially censored at the start of the first further anti-cancer therapy that would not have been prescribed in clinical practice.

Patients in IMROZ experiencing progressive disease (based on investigator assessment) were eligible to discontinue their randomly assigned treatment and were permitted further anti-cancer therapies. Further anti-cancer therapies that are not used in clinical practice in the UK included both crossover patients from Rd to IsaRd in the continuous phase for patients receiving VRd induction therapy, and receipt of subsequent treatments in either treatment arm. The analyses of OS were adjusted to account for the effect of crossover and/or other subsequent treatments not available in NHS clinical practice.

Crossover from Rd to IsaRd and subsequent treatments that are not available in NHS clinical practice

The OS HR from the ITT analysis without adjustment was 0.776 (95% CI; 0.548, 1.099). After adjustment for crossover from Rd to IsaRd and subsequent treatments, the HR improved to 0.724 (95% CI; 0.516, 1.015). There is little difference between the adjusted and unadjusted Kaplan-Meier curves for IsaVRd (Figure 11).

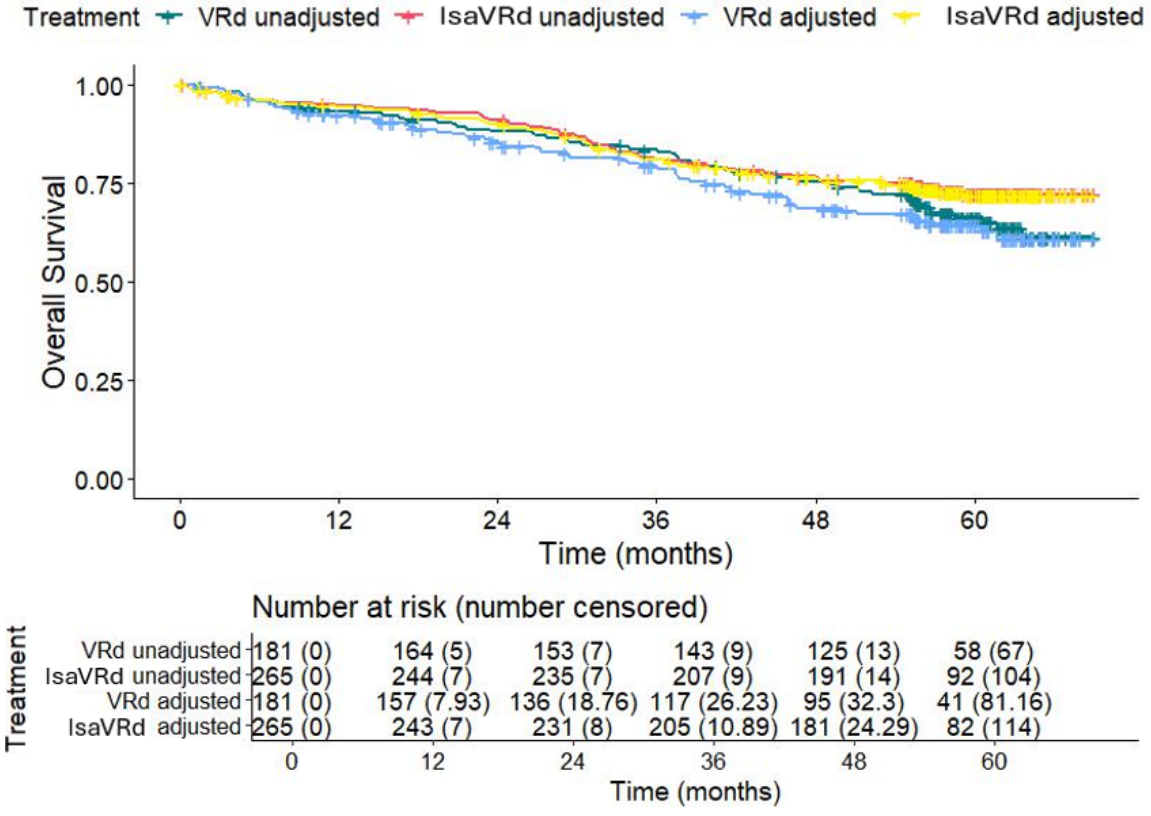
Additionally, the stratified OS hazard ratio between IsaVRd and VRd following adjustment for crossover only from Rd (continuous phase in VRd arm) to IsaRd (continuous phase in IsaVRd arm) was 0.729 (95% CI; 0.521, 1.020) and did not differ from the adjustment for cross-over and subsequent treatments not available in NHS practice (Table 18). The separate analysis on crossover only from Rd to IsaRd is provided in Appendix O.2.2.

Table 18: Overall survival adjusted for crossover from Rd to IsaRd and subsequent treatments that are not used in clinical practice in the UK using IPCW approach – summary

Scenario	Hazard Ratio (stratified; 95% CI)
Unadjusted data	0.776 (0.548, 1.099)
IPCW - Cross over	0.729 (0.521,1,020)
IPCW - Cross over and subsequent therapies not available in NHS clinical practice	0.724 (0.516, 1.015)

Abbreviations: CI, confidence interval; IPCW, inverse probability of censoring weighted; IsaRd, isatuximab, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone.

Figure 11: Overall survival adjusted for crossover from Rd to IsaRd and subsequent treatments that are not used in NHS clinical practice



Abbreviations: IsaRd, isatuximab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone.

The analysis results showed an improved OS HR for IsaVRd compared with VRd after adjusting for biases from subsequent treatments not available in the UK (indicated by a reduced HR). This improvement is due to a lower OS in the VRd arm post-adjustment, while the IsaVRd OS curve showed no difference (Figure 11).

Given that IsaVRd OS is marginally or not affected by adjustments for subsequent therapies not used in NHS clinical practice, and that adjusted OS could introduce uncertainty, the base case of the economic model uses unadjusted IsaVRd OS. Additionally, VRd is not a relevant comparator for the UK. Matching-adjusted indirect comparisons (MAICs) are also used in the base case, and IsaVRd OS does not depend on VRd (Section B.3.3).

B.2.6.1.4 Other efficacy outcomes

Overall response rate

The majority (>90%) of study participants obtained a tumour response during the study treatment. In the ITT population, ORR (includes sCR, CR, VGPR, and PR as assessed by the IRC) was similar in the IsaVRd and VRd groups, with 242 (91.3%) participants in the IsaVRd group and 167 (92.3%) participants in the VRd group, being responders (Table 15).

Time to progression

The median time to progression (TTP) based on IRC assessment was not reached for the IsaVRd group, while it was 59.70 months (CI; 48.164, NC) for the VRd group. The HR indicated a strong treatment effect (0.414 [95% CI; 0.286, 0.598]), consistent with the primary analysis of PFS and a lower percentage of participants in the IsaVRd group vs the VRd group having disease progression events (18.9% vs 36.5%, respectively).

Duration of response

Among responder participants (PR or better based on IRC assessment) in the IsaVRd and VRd groups (242 and 167, respectively), the median duration of response was not reached in the IsaVRd group and was 58.25 months (95% CI; 44.583, not calculated [NC]) in the VRd group.

Time to first response

In the ITT population, the median time to first response was short in both groups: 1.51 months [95% CI; NC, NC] in the IsaVRd group and 1.48 months [95% CI; 1.478, 1.511] in the VRd group.

Time to best response

In the ITT population, TTBR was approximately 1 month longer in the IsaVRd group than in the VRd group (6.51 months [95% CI; 5.651, 6.867] and 5.59 months [95% CI; 4.304, 5.881], respectively).

Of note, the level of best response was generally higher in the IsaVRd group. There were more participants reaching sCR compared with the VRd group. All participants with sCR presented with CR before reaching sCR criteria. As per the protocol and based on 2016 IMWG criteria, sCR required a bone marrow biopsy for clonality assessment, which was not done systematically when needed for some participants, or it was done late for others.

Sustained MRD negativity rate (≥12 months)

The sustained MRD negativity rate (10^{-5} sensitivity level by central laboratory NGS) for at least 12 months in the ITT population was almost twice as high in the IsaVRd group compared with the VRd group (46.8% [95% CI; 0.4066, 0.5300] vs 24.3% [95% CI; 0.1825, 0.3123]) (Table 114 in Appendix M). The OR of IsaVRd vs VRd was 2.729 [95% CI; 1.799, 4.141].

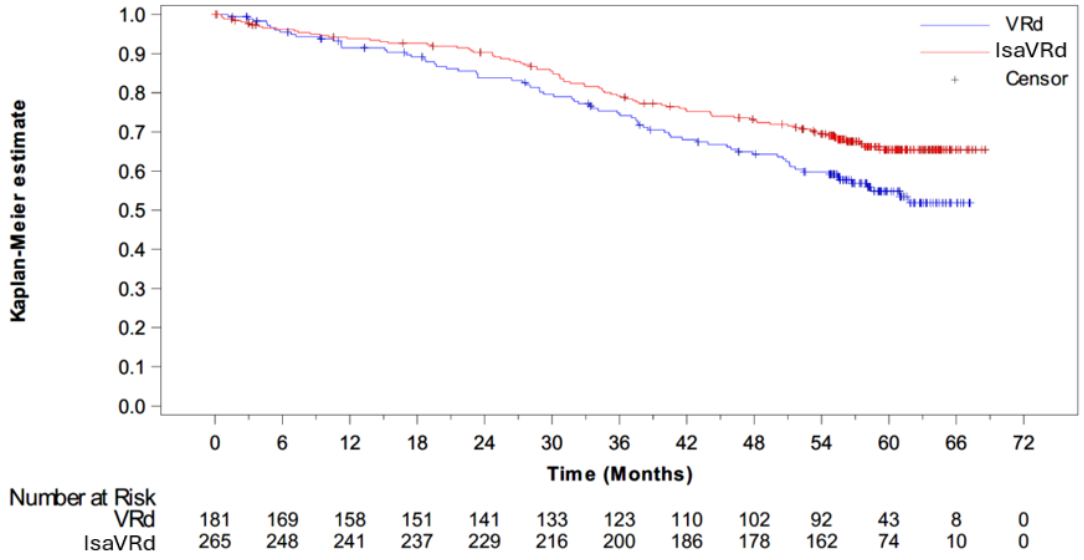
Similarly, the proportion of participants with a MRD negativity rate for at least 6 months was higher in the IsaVRd group compared with the VRd group (50.9% [95% CI; 0.4475, 0.5711] vs 30.9% [95% CI; 0.2429, 0.3822]).

For the 46.8% of the IsaVRd participants having reached sustained MRD negativity for at least 12 months, 35.8% remained MRD-negative for at least 24 months and 25.7% for at least 36 months.

PFS2

At the cut-off date, 19.6% of participants in the IsaVRd group and 44.2% of participants in the VRd group had initiated a further anti-myeloma therapy. The percentage of participants with PFS2 events was 31.7% in the IsaVRd group and 41.4% in the VRd group (Figure 12). While the median PFS2 was not reached in either treatment arm, the PFS2 treatment benefit appears to be maintained during the next treatment line, based on an observed PFS2 HR of 0.697 (95% CI; 0.51, 0.952).

Figure 12: PFS2 based on disease assessment by the investigator – Kaplan-Meier curves by treatment group – ITT population



Abbreviations: CSR, clinical study report; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; ITT, intent-to-treat; PFS, progression-free survival; VRd, bortezomib, lenalidomide, and dexamethasone.
Cut-off date: 26 September 2023. Median follow-up time = 59.73 months.
Source: IMROZ CSR, 2024 (88).

B.2.6.1.5 Additional evidence of clinical benefit

Time to next treatment

In the ITT population, time to next treatment in the IsaVRd group was delayed compared with the VRd group (stratified HR 0.376 [95% CI; 0.265, 0.534]). The HR of time to next treatment was similar to the HR of PFS determined by the IRC (HRs 0.376 and 0.596, respectively), indicating that time to next treatment initiation was consistent with the PFS analysis. The median time to next treatment was not reached in the IsaVRd group and was 63.57 months (range; 48.624, NC) for the VRd group.

Among participants who received further anti-myeloma treatment (52 [19.6%] and 80 [44.2%] participants in the IsaVRd and VRd groups, respectively), the most frequent subsequent therapy given were corticosteroids (100% and 90.0% in the IsaVRd and VRd groups, respectively) and immunomodulators, which were also administered at a similar frequency in the IsaVRd and VRd treatment groups (76.9% and 72.5%, respectively). This included not only the second line of therapy, but all further lines received by the participants. The further anti-myeloma treatment included anti-CD38 monoclonal antibodies in approximately half as many participants in the IsaVRd group than the VRd group (34.6% and 68.8%, respectively). In total, 13.5% (n=7/52) patients at 2L after treatment with IsaVRd received an anti-CD38 therapy. A summary of further anti-myeloma treatments is provided in Table 19. The complete list of regimens used across second, third, and fourth lines by patients from IMROZ is provided in Appendix O.2.1.

Table 19: Summary of further anti-myeloma treatments - ITT population

	IsaVRd (N=265)	**VRd (N=181)**
Number (%) of patients with any further anti-myeloma treatment†	52 (19.6)	80 (44.2)
Number of further regimens		
Number of patients	52	80
Mean (SD)	2.1 (1.4)	1.6 (1.2)
Median	2.0	1.0
Min; Max	1; 7	1; 7
Number of further regimens [n (%)]		
Number of patients	52	80
1	25 (48.1)	53 (66.3)
2	13 (25.0)	16 (20.0)
≥3	14 (26.9)	11 (13.8)

	IsaVRd (N=265)	VRd (N=181)
Main further anti-myeloma treatments by class and agent [n (%)]		
Number of patients	52	80
Alkylating agents	23 (44.2)	23 (28.8)
Bendamustine	1 (1.9)	2 (2.5)
Cyclophosphamide	18 (34.6)	17 (21.3)
Melphalan	9 (17.3)	7 (8.8)
Proteasome inhibitors	40 (76.9)	38 (47.5)
Bortezomib	27 (51.9)	19 (23.8)
Carfilzomib	19 (36.5)	17 (21.3)
Ixazomib	8 (15.4)	6 (7.5)
Immunomodulators	40 (76.9)	58 (72.5)
Iberdomide	1 (1.9)	2 (2.5)
Lenalidomide	16 (30.8)	41 (51.3)
Mezigdomide	1 (1.9)	0
Pomalidomide	24 (46.2)	26 (32.5)
Thalidomide	5 (9.6)	5 (6.3)
Anthracyclins	3 (5.8)	2 (2.5)
Doxorubicin	1 (1.9)	2 (2.5)
Doxorubicin hydrochloride	1 (1.9)	0
Pegylated liposomal doxorubicin hydrochloride	1 (1.9)	0
Corticosteroids	52 (100)	72 (90.0)
Dexamethasone	50 (96.2)	66 (82.5)
Methylprednisolone	1 (1.9)	0
Prednisolone	1 (1.9)	4 (5.0)
Prednisone	4 (7.7)	6 (7.5)
Vinca alkaloids	1 (1.9)	0
Vincristine sulfate	1 (1.9)	0
Antimetabolites	1 (1.9)	2 (2.5)
Azacitidine	0	1 (1.3)
Fludarabine	1 (1.9)	1 (1.3)
Anti-CD38 agents	18 (34.6)	55 (68.8)
Cd38 (clusters of differentiation 38) inhibitors	1 (1.9)	0
Daratumumab	15 (28.8)	30 (37.5)

	IsaVRd (N=265)	VRd (N=181)
Daratumumab;vorhyaluronidase alfa	1 (1.9)	0
Isatuximab	3 (5.8)	29 (36.3)
Anti SLAMF 7 agents	2 (3.8)	0
Elotuzumab	2 (3.8)	0
FcRH5 targeting agents	1 (1.9)	0
Cevostamab	1 (1.9)	0
Anti-CD47 agents	0	1 (1.3)
Magrolimab	0	1 (1.3)
CAR T cell	1 (1.9)	2 (2.5)
Car t-cells nos	1 (1.9)	2 (2.5)
Anti-Bcl-2 Antibody	0	1 (1.3)
Venetoclax	0	1 (1.3)
Other	6 (11.5)	12 (15.0)
Anti-BCMA	4 (7.7)	8 (10.0)
Autologous stem cells nos	0	2 (2.5)
Haematopoietic stem cells nos, autologous	0	1 (1.3)
Radiotherapy	1 (1.9)	0
Sar 442257	1 (1.9)	0
Tocilizumab	1 (1.9)	1 (1.3)

Abbreviations: BCMA, B-cell maturation antigen; Cd38, clusters of differentiation 38; CO, crossover; CSR, clinical study report; IsaRd, isatuximab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; SD, standard deviation; VRd, bortezomib, lenalidomide, and dexamethasone.
Note: for patients from VRd arm that switched to CO IsaRd arm, IsaRd is counted as a further regimen.
Source: IMROZ CSR, 2024 (88).

Time to treatment discontinuation

The results observed in the IMROZ study for TTD are summarised in Figure 13 and Table 20. The median TTD is [redacted] months for the IsaVRd arm and [redacted] months for the VRd arm (difference: [redacted] months). The difference in restricted mean survival is [redacted] months ([redacted] vs [redacted] months in the IsaVRd and the VRd arm, respectively). The unstratified hazard ratio for TTD between IsaVRd and VRd is [redacted] (95% CI; [redacted], [redacted]), which is [redacted] the unstratified hazard ratio for PFS ([redacted]; [redacted]).

Figure 13: Time to discontinuation – IMROZ ITT population – Kaplan–Meier

Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; ITT, intent-to-treat; VRd, bortezomib, lenalidomide, and dexamethasone.

Table 20: Time to discontinuation – IMROZ ITT population – summary

Treatment	Subjects	Events	Censors	Median (Months; 95% CI)	Restricted mean survival (Months; SE)	Hazard ratio (unstratified) (95% CI)
VRd	181	[redacted]	[redacted]	[redacted]	[redacted]	NA (NA, NA)
IsaVRd	263	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; ITT, intent-to-treat; NA, not applicable; SE, standard error; VRd, bortezomib, lenalidomide, and dexamethasone.

B.2.6.1.6 Health-related quality-of-life assessments

EQ-5D-5L

In the IMROZ clinical trial, EQ-5D-5L data were collected on Day 1 of each cycle in the induction phase; there are four cycles of 6 weeks in the induction phase. In the continuous phase, EQ-5D-5L data were collected on Day 1 of each cycle until the end of treatment. The cycle length in the continuous phase was 4 weeks. Additional EQ-5D-5L data were collected at the end of treatment (defined as 30 days after the last investigational medical product administration). The final collection of EQ-5D-5L data

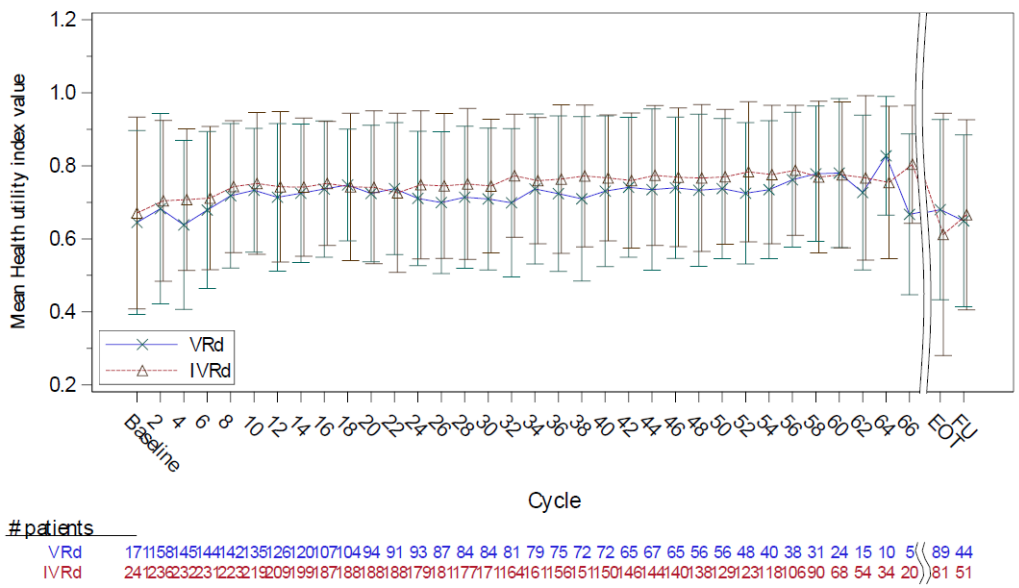
occurred during the follow-up phase at 90 days following the last study treatment administration.

More than 90% of the participants for the 14 first cycles and more than 80% at each cycle completed the EuroQol-5 Dimensions-5 Level (EQ-5D-5L) questionnaire.

Data from the EQ-5D-5L Health State Utility Index suggest an observable trend where the addition of isatuximab to VRd improves the quality of life for patients (Figure 14). Results mapped to EQ-5D-3L and included in the cost-effectiveness model are presented in Section B.3.4.6.

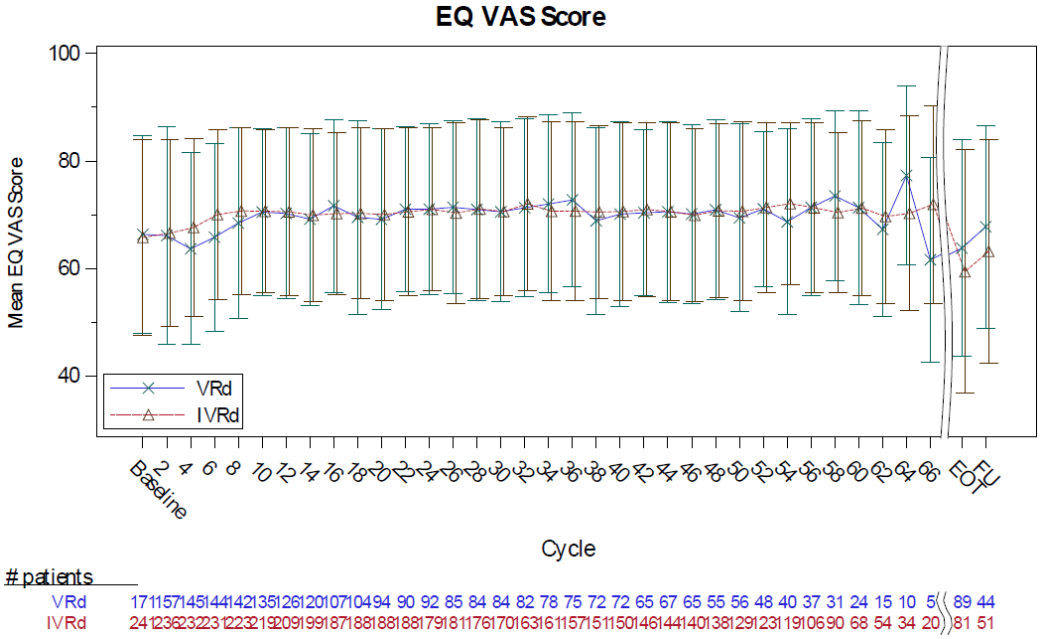
The addition of isatuximab to VRd did not result in a detriment to the QoL of the patient, as assessed by the EQ-5D-5L Visual Analogue Scale. The score remained stable throughout treatment in both groups. There was no negative effect on QoL by the addition of isatuximab when comparing both treatment groups (Figure 15).

Figure 14: EQ-5D-5L – Mean (SD) for HSUV over time – ITT population evaluable for HSUV



Abbreviations: CSR, clinical study report; EOT, end of treatment; EQ-5D-5L, EuroQoL 5-dimension 5-level; FU, follow-up; HSUV, health state utility index value; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; ITT, intent-to-treat; SD, standard deviation; VRd, bortezomib, lenalidomide, and dexamethasone.
A higher score represents a better level of quality of life.
Cut-off date: 26 September 2023.
Source: IMROZ CSR, 2024 (88).

Figure 15: EQ-5D-5L – Mean (SD) for VAS score over time – ITT population evaluable for VAS



Abbreviations: CSR, clinical study report; EOT, end of treatment; EQ-5D-5L, EuroQoL 5-dimension 5-level; FU, follow-up; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; ITT, intent-to-treat; SD, standard deviation; VAS, visual analogue scale; VRd, bortezomib, lenalidomide, and dexamethasone.
A higher score represents a better level of quality of life.
Cut-off date: 26 September 2023.
Source: IMROZ CSR, 2024 (88).

EORTC QLQ-C30

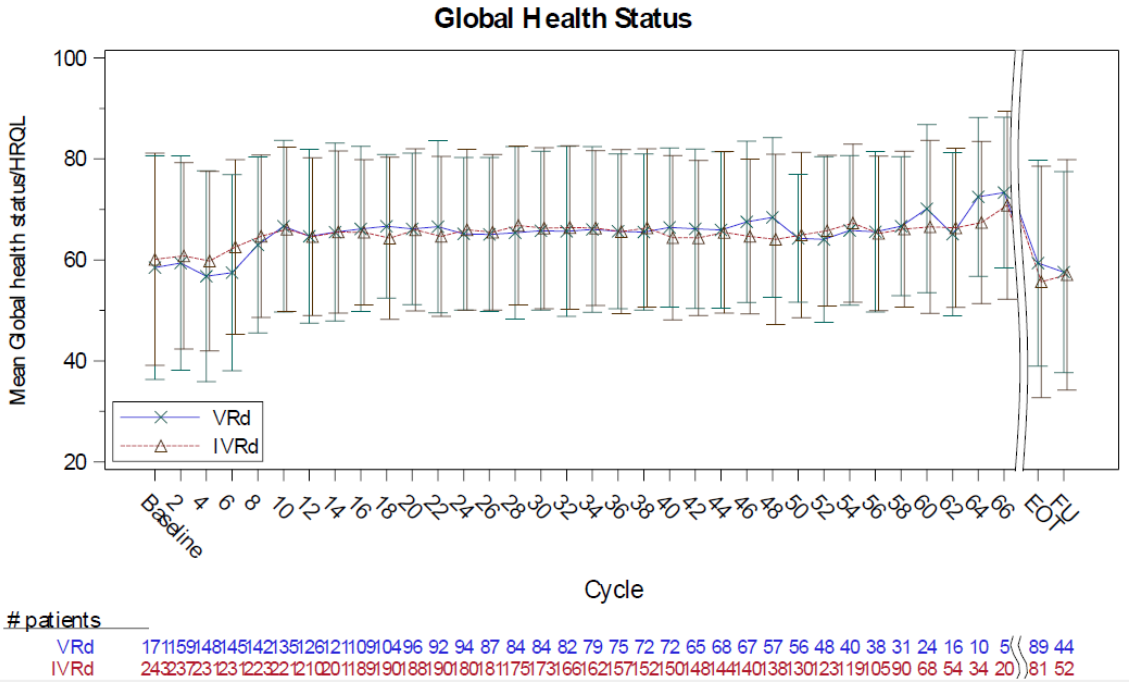
In the IMROZ clinical trial, EORTC QLQ-C30 data were collected on Day 1 of each cycle in the induction phase; there are four cycles of 6 weeks in the induction phase. In the continuous phase, EORTC QLQ-C30 data were collected on Day 1 of each cycle until the end of treatment. The cycle length in the continuous phase was 4 weeks. Additional EORTC QLQ-C30 data were collected at the end of treatment (defined as 30 days after the last investigational medical product administration). The final collection of EORTC QLQ-C30 data occurred during the follow-up phase at 90 days following the last study treatment administration.

Compliance during study treatment was high, with completion of the questionnaire by 90% or more of the participants for at least the 14 first cycles and more than 80% of the participants at each cycle.

Health related quality-of-life – C30 GHS/QoL

Health related quality of life was largely maintained during the treatment period in the VRd and IsaVRd groups as measured by the EORTC QLQ-C30 global health status/quality of life (GHS QoL) score. The GHS QoL score remained stable throughout treatment in both groups. There was no negative effect on the GHS QoL by the addition of isatuximab when comparing both treatment groups (Figure 16).

Figure 16: QLQ-C30 - Mean and standard deviation for global health status score over time - ITT population evaluable for global health status



Abbreviations: CSR, clinical study report; EOT, end of treatment; FU, follow-up; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; ITT, intent-to-treat; QLQ-C30, Quality of Life Questionnaire – Cancer-specific module with 30 items; VRd, bortezomib, lenalidomide, and dexamethasone.
A higher score represents a better level of quality of life.

Cut-off date: 26 September 2023.
Source: IMROZ CSR, 2024 (88).

Functional Scales –C30 Physical, Role, Cognitive, Emotional, and Social Functioning

Despite isolated change scores of at least 10 points observed toward the end of the treatment period for both treatment groups, no clear or consistent patterns were observed on the C30 physical, role, cognitive, emotional, and social functioning scales. Further information is available in Section 5.1.3.2.8.1 in the IMROZ CSR.

Symptom Scales and Items – C30 Fatigue, Nausea/Vomiting, Pain, Dyspnoea, Insomnia, Appetite Loss, Constipation, Diarrhoea, and Financial Difficulties

Despite isolated change scores of at least 10 points for both treatment groups, no clear or consistent patterns were observed on the C30 fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties symptom scales and items. Further information is available in Section 5.1.3.2.8.1 in the IMROZ CSR.

EORTC QLQ-MY20

Compliance during study treatment was very good, with completion of the questionnaire by more than 90% of the participants until Cycle 14, and more than 80% at each cycle.

Despite isolated change scores of at least 10 points for both treatment groups, mostly observed toward the end of the treatment period, no clear or consistent patterns were observed on the MY20 body image, future perspective, disease symptoms, and side effects of treatment scales/items. Further information is available in Section 5.1.3.2.8.1 in the IMROZ CSR.

B.2.7 *Subgroup analysis*

Subgroup analyses of the primary endpoint (PFS) and treatment-emergent adverse events (TEAEs) were conducted in IMROZ.

B.2.7.1 *Methodology*

Primary endpoint subgroups

The primary endpoint (PFS) was analysed for the following pre-planned subgroups in IMROZ:

- Age (IRT): <70 years and ≥70 years
- Age: <70 years, ≥70 years to <70 years, and ≥75 years
- Gender: Male and Female
- Race: Caucasian and Other
- Geographical region: Europe/North America, Asia, and Other countries/regions[b]
- Asian region vs other countries: Asia and other countries/regions[c]
- Baseline ECOG PS: 0 or 1 and >1
- Baseline creatinine clearance (Modification of Diet in Renal Disease [MDRD]): <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2
- Haemoglobin at baseline: <10 g/dL and ≥10 g/dL

Post-hoc analysis of frailty subgroups

Analyses by frailty subgroup includes PFS and adverse events.

Exploratory analysis of high-risk cytogenetic population

Analyses by for high-risk cytogenetic populations.

B.2.7.2 *Statistical information*

Primary endpoint subgroups

For each pre-defined factor among the demographic/baseline characteristics defined in Section B.2.7.1, PFS was analysed using a non-stratified Cox proportional hazards model with terms for the factor, treatment, and their interaction. The test of the interaction was performed at the 10% alpha level.

[b] Other countries include Australia, New Zealand, Mexico, Turkey, and Russian Federation.

[c] Other countries include Australia, Belgium, Czechia, Denmark, France, Germany, Greece, Italy, Lithuania, Mexico, New Zealand, Poland, Portugal, Russian Federation, Spain, Sweden, Turkey, and the United States of America.

B.2.7.3 *Results*

B.2.7.3.1 PFS subgroup analysis

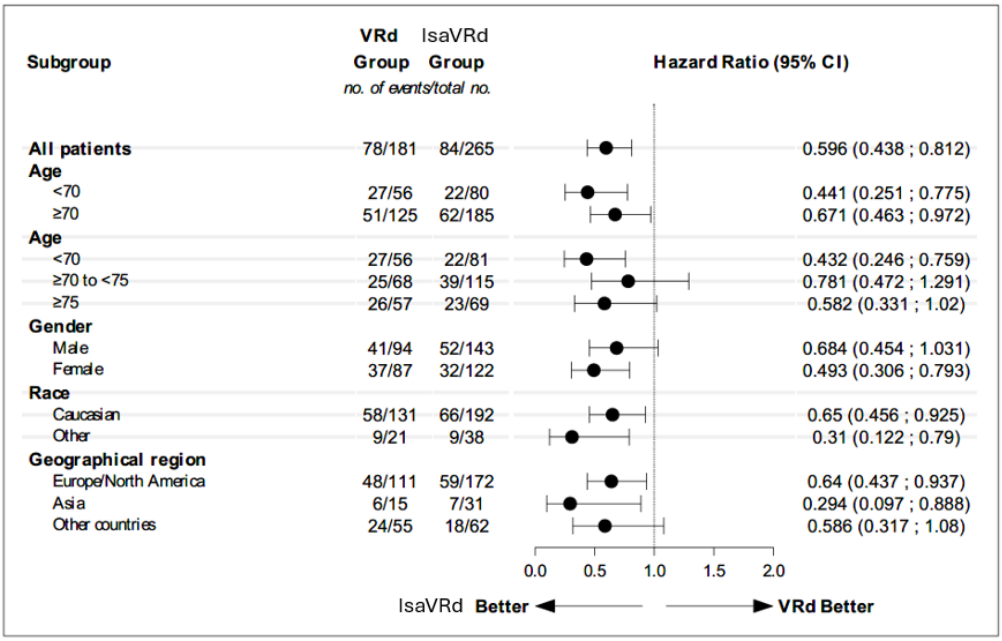
Subgroup analyses of PFS were conducted when at least 10 participants were included in each treatment group within a subgroup. Subgroup analyses for the majority of the prespecified subgroups, including poor prognosis subgroups, showed a positive treatment effect favouring IsaVRd over VRd, consistent with the overall PFS analysis (Section B.2.6.1.1). Forest plots of the subgroup analyses by demographic characteristics are provided in Figure 17 and Figure 18.

The majority of prespecified subgroup analyses showed no significant interaction at the 10% level between treatment groups and subgroups of stratification factors, demographic characteristics, or participants' baseline characteristics, indicating an overall consistent treatment effect across those subgroups.

Of note, in the subgroup of MM type at study entry (IgG versus Non-IgG), in the subgroup of Plasmacytoma disease per IRC (Extramedullary disease versus Only paramedullary disease vs No plasmacytoma disease), and in the subgroup of chromosomal 1q21+ abnormality, the p-value for interaction is below 10%, suggesting there is some difference of the treatment effect across those subgroups. The effect of IsaVRd over VRd seems to be stronger respectively in the IgG subgroup, Extramedullary disease subgroup, and in participants with chromosomal 1q21+ abnormality.

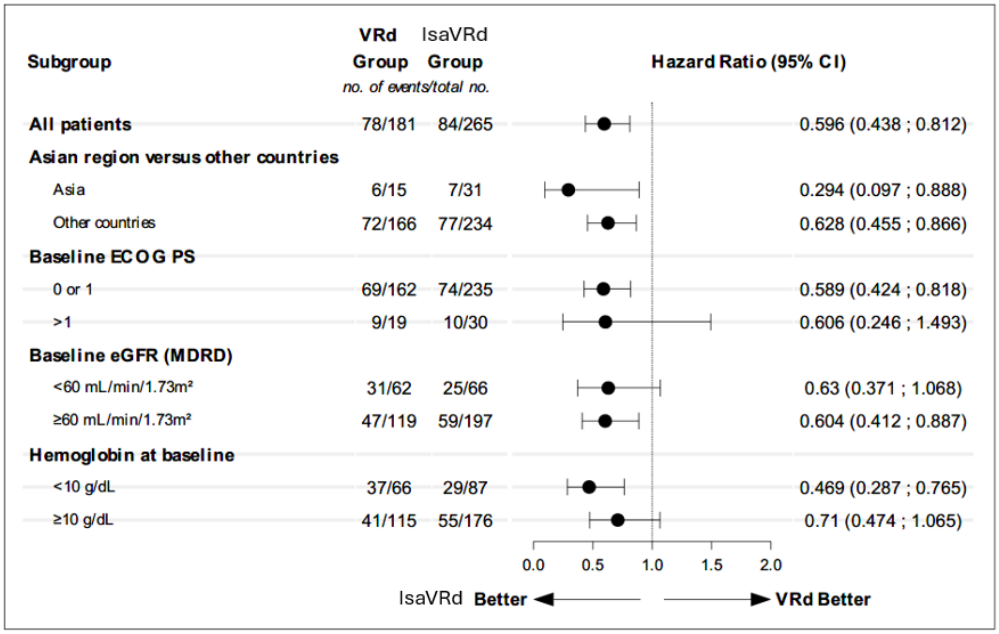
Additional information is provided in Appendix E.1.1.

Figure 17: PFS based on disease assessment by the IRC – Subgroup analyses 1 (forest plot) – By demographics/baseline characteristics – ITT population



Abbreviations: CI, confidence interval; CSR, clinical study report; IRC, Independent Response Committee; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; ITT, intent-to-treat; PFS, progression-free survival; VRd, bortezomib, lenalidomide, and dexamethasone.
Cut-off date: 26 September 2023.
Source: IMROZ CSR, 2024 (88).

Figure 18: PFS based on disease assessment by the IRC – Subgroup analyses 2 (forest plot) – By demographics/baseline characteristics – ITT population



Abbreviations: CI, confidence interval; CSR, clinical study report; ECOG; Eastern Cooperative Oncology Group; IRC, Independent Response Committee; ITT, intent-to-treat; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; MDRD, Modification of Diet in Renal Disease; PFS, progression-free survival; PS, performance status; VRd, bortezomib, lenalidomide, and dexamethasone.
Cut-off date: 26 September 2023.
Source: IMROZ CSR, 2024 (88).

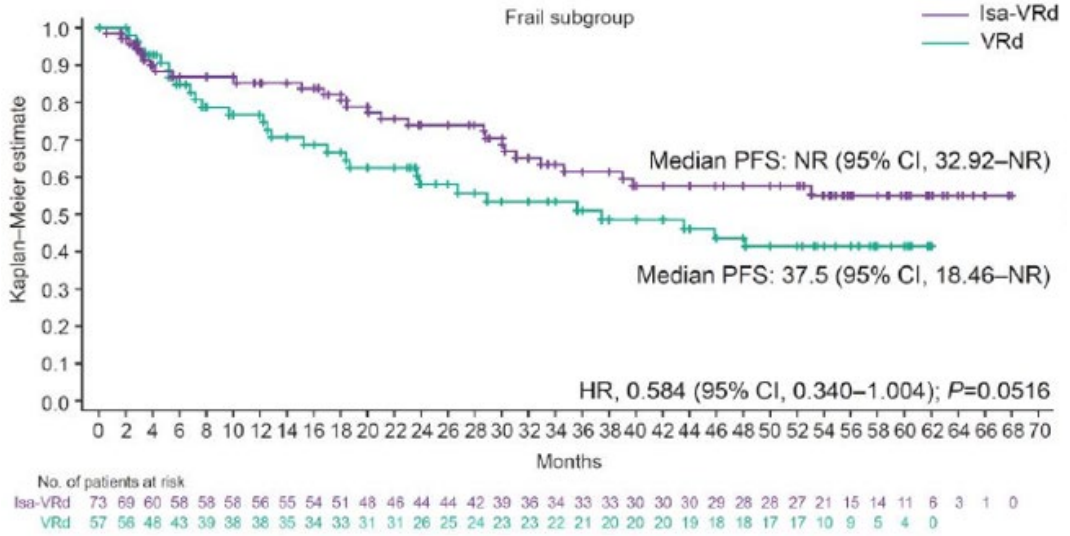
PFS post-hoc subgroup analysis (Frailty)

A post-hoc frailty subgroup analysis of the IMROZ study was conducted to evaluate the use of IsaVRd followed by IsaRd compared with VRd followed by Rd across frail and non-frail subgroups. The proportion of frail and non-frail patients in IMROZ was determined by the IMWG frailty score. This simplified frailty score determines outcomes based on frailty using scores for age, Charlson Comorbidity Index (CCI), and Eastern Cooperative Oncology Group Performance Status (ECOG PS). Using this simplified frailty score, frailty scores at baseline were calculated based on age, modified CCI (calculated using medical history at baseline), and ECOG PS. Patients with a frailty score of 0/1 were considered non-frail, and those with scores ≥2 were classified as frail.

Using the simplified frailty score and regardless of age cutoff, 29% of patients were frail (28% IsaVRd; 32% VRd), and 70% were non-frail (72% IsaVRd; 67% VRd); 1% had missing data.

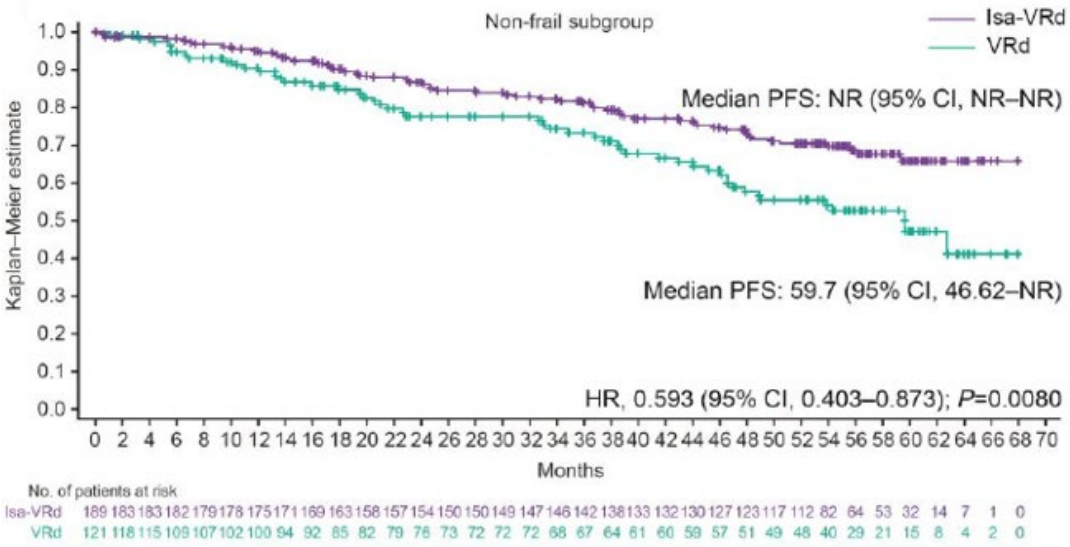
At a median follow-up of 59.7 months, IsaVRd led to improved median PFS vs VRd in both frail and non-frail subgroups (95). Among frail patients, the 60-month PFS rate was reported in 55.2% of patients treated with IsaVRd compared with 41.3% of patients treated with VRd (HR: 0.584 [95% CI; 0.340, 1.004]; p=0.052) (Figure 19). Among non-frail patients, the 60-month PFS rate was reported in 66.0% and 47.3% of patients treated with IsaVRd and VRd, respectively (HR: 0.593 [95% CI; 0.403, 0.873]; p=0.008) (Figure 20).

Figure 19: Kaplan-Meier curves of progression-free survival for frail patients



Abbreviations: CI, confidence interval; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; NR, not reached; PFS, progression-free survival; VRd, bortezomib, lenalidomide and dexamethasone.

Figure 20: Kaplan-Meier curves of progression-free survival for non-frail patients



Abbreviations: CI, confidence interval; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; NR, not reached; PFS, progression-free survival; VRd, bortezomib, lenalidomide and dexamethasone.

The rates of TEAEs leading to definitive discontinuation were similar between arms in both the frail and non-frail subgroups (Table 21).

Table 21: Overview of TEAEs in the safety population by patient-year

	Frail (N=129)				Non-frail (N=309)			
	IsaVRd (n=72)		VRd (n=57)		IsaVRd (n-188)		VRd (n=121)	
	N (%)	Event rate per patient-year	N (%)	Event rate per patient-year	N (%)	Event rate per patient-year	N (%)	Event rate per patient-year
Patients with any TEAE	72 (100)	16.761	56 (98.25)	29.991	187 (99.47)	19.588	119 (98.35)	18.727
Patients with any Grade ≥3 TEAE	66 (91.67)	2.221	49 (85.96)	3.248	172 (91.49)	1.832	100 (82.64)	2.141
Patients with any Grade 5 TEAE*	9 (12.50)	0.975	5 (8.77)	1.979	20 (10.64)	0.509	5 (4.13)	0.416
Patients with any TEAE leading to definitive treatment Discontinuation	21 (29.17)	0.957	20 (35.09)	0.965	39 (20.74)	0.530	27 (22.31)	0.525
Patients with any treatment-emergent SAE†	56 (77.78)	1.051	47 (82.46)	1.340	130 (69.15)	0.989	74 (61.16)	1.296

Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; SAE, serious adverse event; TEAE, treatment-emergent adverse event; VRd, bortezomib, lenalidomide, and dexamethasone.

* Grade 5 TEAEs in the frail IsaVRd arm included 1 death, 1 multiple organ dysfunction syndrome, 1 sudden death, 2 COVID-19 pneumonia, 1 Candida sepsis, 1 pneumonia, 1 pneumonia pseudomonal, 1 tumour lysis syndrome, 1 renal tubular acidosis, and 1 respiratory failure. These were not mutually exclusive.

† TEAEs with a start date before the operational cutoff date and becoming serious after the operational cutoff date were not counted as serious TEAEs in this analysis.

B.2.7.3.2 Exploratory efficacy endpoint

High-risk cytogenetic population

High-risk cytogenetic status was defined as the presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16). An abnormality was considered positive if it was present in at least 30% of analysed plasma cells, except for del(17p) where the threshold was at least 50%.

In addition to the 3 chromosomal abnormalities (del(17p), t(4;14), and t(14;16)) assessed by fluorescence in situ hybridisation (FISH) at baseline to determine R-ISS stage, which is a stratification factor, 1q21+ (both gain and amplification) was assessed and correlated with parameters of clinical response. This abnormality was considered positive if at least three copies were present in at least 30% of analysed plasma cells.

As the subgroup with high-risk cytogenetics consists of patients with several potential chromosomal abnormalities, a further analysis was performed to characterise the treatment effect within the individual chromosomal abnormalities. HR provided for t(14;16) is not interpretable as there were fewer than 10 participants with this chromosomal abnormality in the study.

Improvement in PFS in participants with chromosomal t(4;14) abnormality (HR: 0.795; [95% CI; 0.333, 1.896]) or in participants with chromosomal 1q21+ abnormality (HR: 0.407; [95% CI; 0.253, 0.653]), respectively, were consistent with the analysis for all participants (HR: 0.596; [95% CI; 0.406, 0.876]). Improvement in PFS was also consistent in the participants with chromosomal 1q21+ abnormality combined with translocation abnormalities (HR: 0.570; [95% CI; 0.195, 1.665]).

Further details are available in Section 5.1.4.1 of the CSR.

B.2.8 *Meta-analysis*

Not applicable.

B.2.9 *Indirect and mixed treatment comparisons*

As per the decision problem (Section B.1.1), the comparators for IsaVRd are DRd, Rd, VCd, and VMP. In the absence of comparative evidence from head-to-head clinical trials, indirect treatment comparisons (ITCs) are necessary to estimate the relative efficacy of IsaVRd vs comparators.

Following a systematic literature review (Appendix D.1) and feasibility assessment (Appendix D.3), a stepwise approach was undertaken to determine the most appropriate method to compare IsaVRd with the relevant comparators.

First, a network meta-analysis was considered for the comparison to DRD, Rd, and VMP. However limitation of this approach became apparent with the trial used to connect IsaVRd into the network for the remaining comparators, which are discussed below. Consequently, an unanchored MAIC and IPW were conducted as they provided the most suitable approach to assess comparative effectiveness evidence and is subsequently used in the economic analyses (see Section B.2.9).

In addition to comparative efficacy, the results of the ITCs were used to support cost-effectiveness analysis of IsaVRd versus other comparators.

B.2.9.1 *Search strategy*

Please see Section B.2.1 for the method used to identify evidence on the efficacy and safety of comparator treatments of relevance to the decision problem.

B.2.9.2 *Study selection*

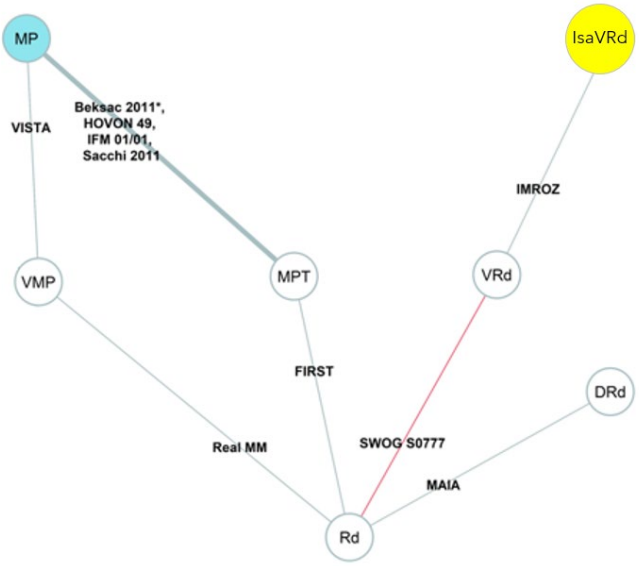
Please refer to Section B.2.1.1.2 for details on the study selection.

B.2.9.2.1 Feasibility assessment of ITC

In total, 76 RCTs were identified from the clinical SLR. Of these, 33 were in the TI population, 30 were in the TE population, six had a mixture of both transplant eligible and ineligible patients, and the transplant status was unclear in seven studies.

Following a review of the connectivity of the evidence base for the UK context, 10 studies (IMROZ plus 9 comparator studies) informed the network of evidence. MP and MPT were added to improve network connectivity, even though they are not considered relevant comparators. This recommendation is due to limitations around the Real MM trial. Results of the inconsistency assessment show that for each treatment comparison (MPT vs MP, Rd vs MPT, VMP vs MP and VMP vs Rd), the direct evidence does not align with the indirect evidence. Notably, the estimate from the NMA is closer aligned to the direct evidence for all comparisons except VMP versus Rd, likely due to the large uncertainty seen in results for the RCT that provides head-to-head evidence for VMP versus Rd (i.e. Real MM). Real MM is expected to be the source of inconsistency in the NMA, as a highly favorable OS HR was observed for VMP compared with Rd (HR = 0.53 [95% CI: 0.26, 1.07]), although the result was not statistically significant. The highly favorable result may be due to the short length of follow-up (median follow-up of 19 months) and few OS events. Additional information on inconsistency analyses are presented in Appendix D.3.1.7, Tables 27, 28, 31, and 32.

Figure 21: UK Network diagram



Abbreviations: DRd, daratumumab, lenalidomide and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; ITC, indirect treatment comparison; MP, melphalan and prednisone; MPT, melphalan, prednisone and thalidomide; Rd, lenalidomide and dexamethasone; VMP, bortezomib, melphalan and prednisone; .
Notes: * Beksac 2011 included in OS network only due to lack of reported PFS data. ** OCTANS did not report Kaplan–Meier curves for OS. Yellow highlight indicates the intervention of interest for ITCs (IsaVRd). The red line represents the link based solely on non-randomised proxy data from SWOG S0777.

The network is limited by the inclusion of a non-randomised subgroup from the SWOG S0777 trial, used as a proxy for the TI population to allow network connectivity (96). This introduces substantial biases due to the following reasons:

- The trial enrolled patients across the entire first-line NDMM spectrum. Outcome data were not reported specifically for the TI subgroup relevant to this decision problem but were instead categorised by age ('<65 years' vs '≥ 65 years'), intent to transplant ('yes' vs 'no'), and actual transplant received ('yes' vs 'no'). The subgroup of patients aged ≥65 years could be the only potential appropriate proxy for a TI patient group analysis, however, since transplant eligibility is not solely defined by age, this subgroup may not fully represent the TI population (97). In addition, the number of patients who reported no intent to transplant at baseline in SWOG-S0777 was lower than the total number of patients in the subgroup of patients aged ≥65 years: 106 Rd patients were aged ≥65 years whereas 72 patients had no intent to transplant, and 91 VRd patients were aged ≥65 years but 73 had no intent to transplant. This suggests that at least 32% (n=34/106) and 20% (n=18/91) of Rd and VRd patients in the age ≥65 years subgroup had an intent to transplant. The exact number of patients who actually received a transplant in this age group remains unknown (96).

- Randomisation was not preserved between treatment arms within this subgroup, as the trial was not stratified by age. This leads to imbalances in patient characteristics between treatment arms, biasing the estimate of relative treatment effects. Stratified HRs are available for OS and PFS and can be used as an alternative. This option was explored following the decision problem meeting where the EAG highlighted the need to use a randomised subgroup. In this case, the group of patients '≥65 years' is not randomised and results should be interpreted with caution. A randomized analysis is generally more robust for causal inference. The stratified HRs for OS and PFS did not include age as a stratification factor. Consequently, residual confounding may exist, as the stratified analysis might not fully account for the influence of age on treatment effects.

- Bortezomib (V) was administered intravenously in SWOG S0777, causing resultant neuropathy; this resulted in a large proportion (23%) of patients prematurely discontinuing VRd induction treatment (98). As such, OS and PFS outcomes for the VRd arm may be underestimated and confounded by early treatment discontinuation and may not be reliable.

Due to these potential limitations involved with including this study in the network, an NMA would likely produce unreliable relative efficacy estimates for IsaVRd vs each treatment. Excluding SWOG S0777 from the network causes IMROZ and IsaVRd to

become disconnected from the wider evidence base as IMROZ does not have a common comparator with any other trial. Therefore, an unanchored MAIC was required for the ITC as the base case for this submission.

A standard NMA was conducted as a scenario analysis (Section B.3 and Appendix D.3). A parametric NMA that allows a time-varying HR over time was not considered appropriate due do the lack of randomisation. Indeed, in addition to limitations previously described, using Kaplan-Meier curves from a non-randomised subgroup may result both unreliable HR and incorrect direction of the treatment effect over time.

B.2.9.2.2 Evidence base for ITC – MAICs and IPW

In total, five trials were considered for unanchored MAIC. These included the MAIA, ALCYONE and FIRST clinical trials (Table 22).

Table 22: Studies included and excluded from MAICs for relevant comparators

Treatment	Studies selected for MAIC	Excluded studies with rationale for exclusion
DRd	MAIA	None – MAIA was the only study available for DRd
Rd	• MAIA • FIRST*	• Real MM – outcomes reported for Real MM were based on limited follow-up (19 months) meaning OS and PFS data are immature • SWOG S0777 – relevant outcome data were not available for the subgroup of TI patients
VMP	ALCYONE	• OCTANS – ALCYONE was preferred over OCTANS as ALCYONE reported Kaplan–Meier curves for both OS and PFS whereas OCTANS only reported PFS. In addition, outcomes for ALCYONE were based on a longer median follow-up time than OCTANS (74.7 months compared with 41.2 months, respectively) • Real MM – outcomes reported for Real MM were based on limited follow-up (median follow-up: 19 months) meaning OS and PFS data are immature • UPFRONT – patients in UPFRONT received bortezomib maintenance therapy which does not align with the EMA and FDA recommended treatment regimen for VMP • VISTA – ECOG PS was not reported so could not be adjusted for in MAICs. As ECOG PS was identified as a prognostic factor, not adjusting for this characteristic may lead to biased ITC results as unobserved imbalances may occur. Furthermore, outcomes for ALCYONE (the selected study) were based on a longer median follow-up time than VISTA (74.7 months compared with 16.3 months, respectively)

Abbreviations: DRd, daratumumab, lenalidomide and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EMA, European Medicines Agency; FDA, Food and Drug Administration; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; TI, transplant ineligible; VMP, bortezomib, melphalan and prednisone.
Notes: *The continuous Rd arm from FIRST was used for MAIC as dosing aligned with EMA and FDA licensing; the Rd 18-cycle arm was excluded.

With respect to VCd, no RCTs were identified from the clinical SLR to support an ITC versus VCd. Although an RCT investigating VCd (AMaRC 03-16) was identified, no relevant outcome data were available so it could not be used for ITCs. A clinical SLR of non-RCTs and observational studies was also conducted (90). The results of this second SLR found that no study was deemed suitable for ITCs due to one or more of the following reasons:

- No study included a suitable common comparator with IMROZ
- Not investigating a transplant-ineligible population
- Not being conducted in the UK, Canada, US, or Western Europe
- Insufficient sample size (i.e. < 30 patients), which will increase uncertainty around relative treatment effect estimates – therefore, an arbitrary cut-off of 30 patients was applied
- Insufficient reporting of baseline characteristics required for unanchored MAIC, either due to missing data or lack of reported characteristics
- Lack of reported Kaplan–Meier curves for OS and/or PFS

Therefore, the following alternative sources of evidence were considered to inform the comparison with VCd:

- Individual-patient data (IPD) from a retrospective, observational cohort study conducted using data from the Flatiron Health Multiple Myeloma Enhanced DataMart, which comprised de-identified US patient-level data (PLD) for patients with MM, including newly diagnosed patients (99)
- NCRAS data from the UK were available. However, PLD were not available for this source. Based on clinician feedback, this source was deemed inappropriate due to heterogeneity of patients (100)

Flatiron data source was identified as the most appropriate source due to the availability of IPD for the VCd-treated patients (101). Availability of PLD for IMROZ and the Flatiron data allowed inverse probability weighting (IPW) to be conducted. Compared with MAIC, IPW is a more robust population-adjustment method because:

- IPW can balance populations based on individual patient characteristics rather than summary characteristics, allowing randomisation to be mimicked more accurately with a smaller loss of sample size and therefore increased power in subsequent analyses
- It is easier to adjust for all relevant prognostic factors and effect modifiers as analyses do not rely on the reporting of characteristics for comparator studies (although information must be collected in trials). Additionally, imputation methods can be used to mitigate limitations around missing baseline characteristics
- The comparator population can be matched to the IMROZ population with regard to patient baseline characteristics, rather than the other way round as in a MAIC

A summary of the data sources used for MAIC and IPW in relation to UK studies is provided in Table 23.

Table 23: Summary of data source candidates for MAIC and IPW

Treatment	Study/data source	Sample size	Study design	Country	OS data source	PFS data source
IsaVRd	IMROZ	265	RCT, open-label, Phase III	Multicentre, international	Individual patient-data (88)	Individual patient-data (88)
Unanchored MAIC						
DRd	MAIA	368	RCT, open-label, Phase III	Multicentre, international	TA917 (33)	Kumar et al. 2022 (102)
VMP	ALCYONE	356	RCT, open-label, Phase III	Multicentre, international	Mateos et al. 2022 (103)	Mateos et al. 2022 (103)
Rd	MAIA	369	RCT, open-label, Phase III	Multicentre, international	TA917 (33)	Kumar et al. 2022 (102)
	FIRST	535	RCT, open-label, Phase III	Multicentre, international	Facon et al. 2018 (104)	Facon et al. 2018 (104)
IPW						
VCd	Flatiron data source	249	Retrospective cohort study	US	Individual patient-data (105)	Individual patient-data (105)

Abbreviations: DRd, daratumumab, lenalidomide and dexamethasone; IPW, inverse probability weighting; IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; Rd, lenalidomide and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan and prednisone.

B.2.9.3 *Methodology*

The methodology for the ITCs, including MAIC, IPW and standard NMA analyses, is provided in Appendix D.3. Information on the evidence base for the NMA, the methodology and results of the NMA, the MAIC results, and the IPW results is also available in Appendix D.3.

B.2.9.4 *Results*

B.2.9.4.1 MAICs

Results for IsaVRd vs DRd, IsaVRd vs VMP, and IsaVRd vs Rd are presented following MAIC analysis. Results for IsaVRd vs VCd are presented following inverse probability weighting (IPW) analysis. Further results are provided in Appendix D.3.

IsaVRd vs DRd (MAIA)

The comparison incorporating MAIA results is preferred because it is the more recent trial compared with the FIRST trial. Results from FIRST are provided in Appendix D.3.2.

MAICs were conducted to estimate the comparative efficacy between IsaVRd and DRd using IMROZ and MAIA, respectively. Analyses were conducted using all available characteristics identified as potential prognostic factors or effect modifiers: age, ISS stage, ECOG PS, cytogenetic risk, creatinine clearance and MM type. The effective sample size (ESS) of the weighted IsaVRd population was 177 patients after matching, which was 67% of the original sample size (N = 265), suggesting reasonable population overlap (Table 37 in Appendix D.3.2).

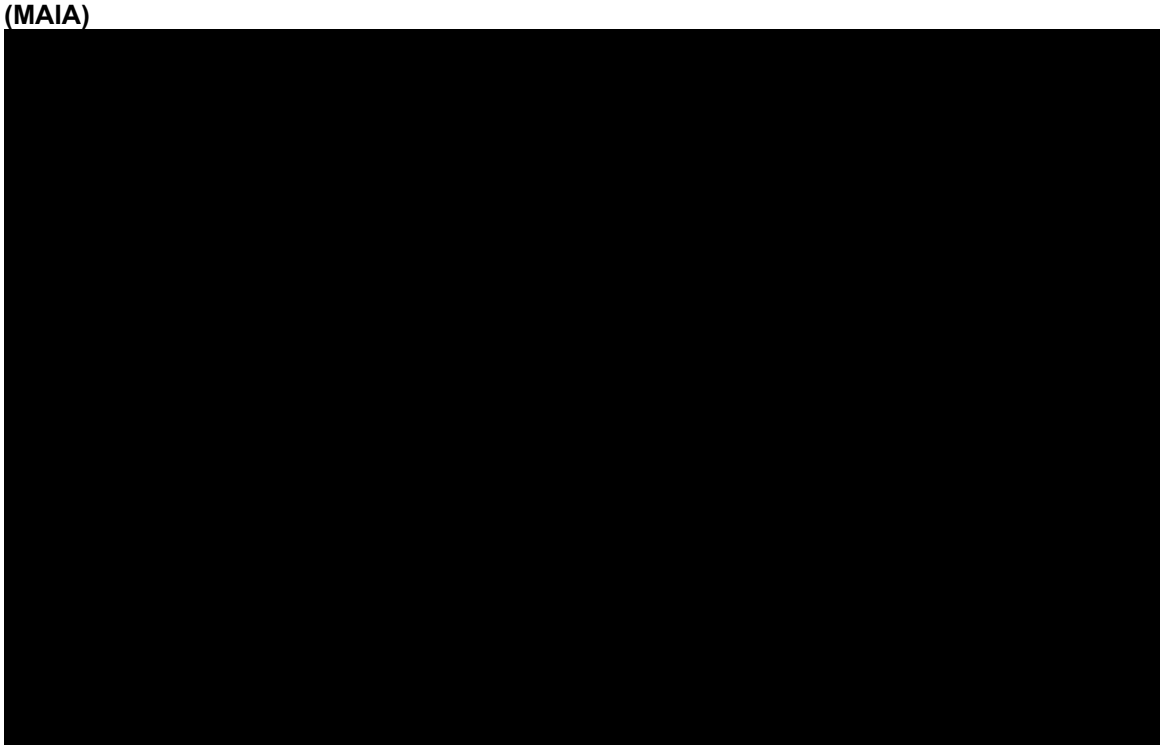
The patient baseline characteristics for IsaVRd and DRd before and after matching are provided in Appendix D.3.3. Patient populations with respect to the matching variables were well-balanced following adjustment.

Additional results for weight histograms, PH assessments, bootstrapped HRs, and weighted PSM model fit statistics are provided in Appendix D.3.2.2.9.

PFS

The MAIC of IsaVRd versus DRd suggested that the relative treatment effect between IsaVRd and DRd was slightly less when adjusting for differences in patient characteristics as shown by the smaller difference in the Kaplan–Meier curves (Figure 22).

Figure 22: Kaplan–Meier plot of PFS before and after MAIC – IsaVRd (IMROZ) vs DRd (MAIA)



Abbreviations: DRd, daratumumab, lenalidomide and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; ITC, indirect treatment comparison; PFS, progression-free survival.

Results are provided in Table 24. For the standard MAIC, which estimates constant HRs, the HR increased from [redacted] (95% CI; [redacted]) in the unadjusted analysis to [redacted] (95% CI; [redacted]) for the MAIC using bootstrapping with percentile CI, which indicates a

statistically significant improvement in PFS for IsaVRd versus DRd. Additional results are provided in Appendix D.3.2.

Table 24: Hazard ratios for progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA)

Method	HR (95% CI)
HR (95% CI) from unadjusted Cox model	[redacted]
HR (95% CI) from weighted Cox model	[redacted]
Bootstrap median HR (95% CI)	[redacted]

Abbreviations: CI, confidence interval; DRd, daratumumab, lenalidomide and dexamethasone; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; ITC, indirect treatment comparison.
Notes: HR <1 favours IsaVRd. Results are considered statistically significant if 1 does not fall within the 95% CI. The bootstrapped HRs show an approximately normal distribution, so the 95% CI based on the 2.5th and 97.5th percentiles is considered reliable for estimating the uncertainty.

OS

The relative treatment effect between IsaVRd and DRd was reduced following adjustment, shown by the smaller difference in the Kaplan–Meier curves (Figure 23).

Figure 23: Kaplan–Meier plot of OS – IsaVRd (IMROZ) vs DRd (MAIA)

Abbreviations: DRd, daratumumab, lenalidomide and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; ITC, indirect treatment comparison; OS, overall survival.

Results are provided in Table 25. In the standard MAIC, which estimates a constant HR, the HR increased from [redacted] (95% CI; [redacted]) in the unadjusted analysis to [redacted] (95% CI; [redacted]) for the MAIC using bootstrapping with percentile CI. The MAIC HR shows a numerical reduction in the hazard of death for IsaVRd but there is no evidence of a

statistically significant treatment effect as the 95% CI includes 1. Additional results are provided in Appendix D.3.2.

Table 25: Hazard ratios for OS – IsaVRd (IMROZ) vs DRd (MAIA)

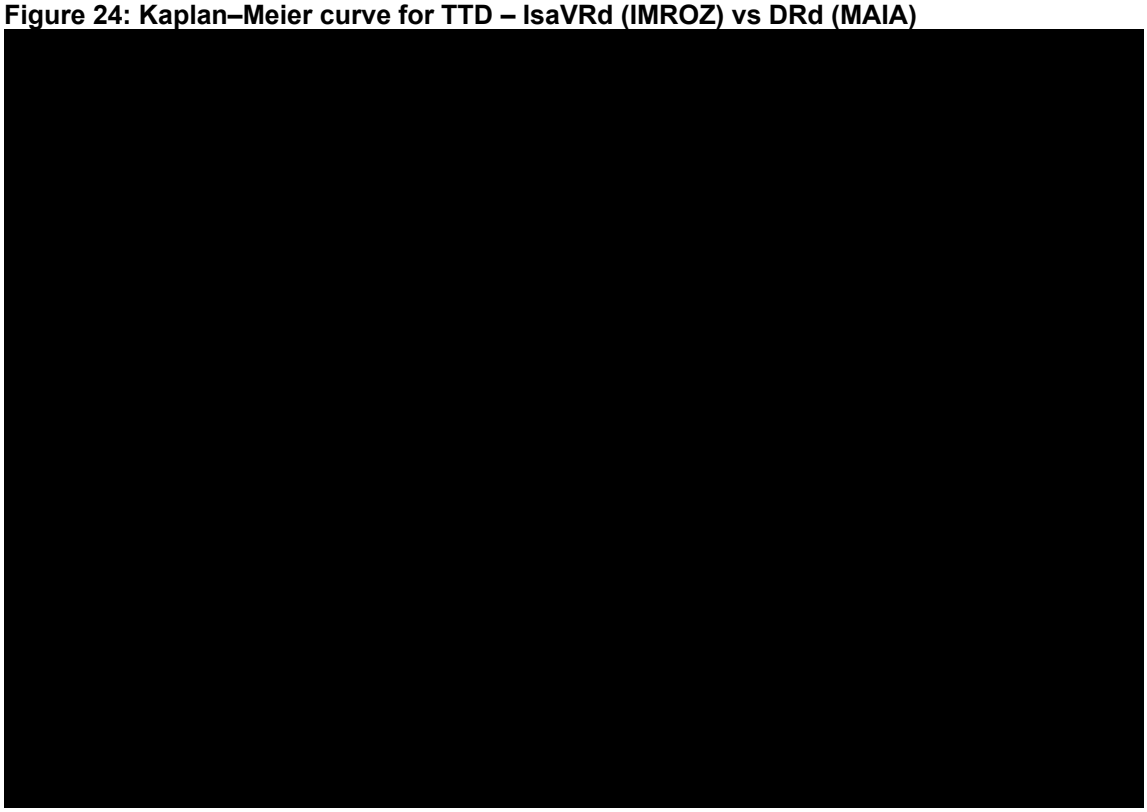
Method	HR (95% CI)
HR (95% CI) from unadjusted Cox model	[redacted]
HR (95% CI) from weighted Cox model	[redacted]
Bootstrap median HR (95% CI)	[redacted]

Abbreviations: CI, confidence interval; DRd, daratumumab, lenalidomide and dexamethasone; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; ITC, indirect treatment comparison; OS, overall survival.
Notes: HR <1 favours IsaVRd. Results are considered statistically significant if 1 does not fall within the 95% CI. A histogram of the bootstrapped HRs shows an approximate normal distribution; therefore, the 95% CI based on the 2.5th and 97.5th percentiles is deemed a reliable method for estimating the uncertainty.

TTD

The relative treatment effect between IsaVRd and DRd was reduced following adjustment, shown by the smaller difference in the Kaplan–Meier curves (Figure 24). Additional information is provided in Appendix D.3.2.

Figure 24: Kaplan–Meier curve for TTD – IsaVRd (IMROZ) vs DRd (MAIA)



Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; TTD, time to discontinuation.

Results are provided in Table 26. In the standard MAIC, which estimates a constant HR, the HR increased from [redacted] (95% CI; [redacted] in the unadjusted analysis to [redacted] (95% CI; [redacted]) for the MAIC using bootstrapping with percentile CI. The MAIC HR shows

a numerical increase in the hazard of death for IsaVRd but there is no evidence of a statistically significant treatment effect as the 95% CI includes 1.

Table 26: Hazard ratios for TTD – IsaVRd (IMROZ) vs DRd (MAIA)

Method	Hazard ratio (95% CI)
HR (95% CI) from unadjusted Cox model	[redacted]
HR (95% CI) from weighted Cox model	[redacted]
Bootstrap median HR (95% percentile CI)	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; SE, standard error.
Notes: Results are considered statistically significant if 1 does not fall within the 95% CI. The bootstrapped HRs show an approximately normal distribution, so the 95% CI based on the 2.5th and 97.5th percentiles is considered reliable for estimating the uncertainty (highlighted in grey).

IsaVRd vs Rd (MAIA)

The comparison incorporating MAIA results is preferred for consistency with DRd and because MAIA is the more recent trial compared with the FIRST trial. Results from FIRST are provided in Appendix D.3.2.

MAICs were conducted to estimate the comparative efficacy between IsaVRd and Rd using IMROZ and MAIA, respectively. Analyses were conducted using all available characteristics identified as potential prognostic factors or effect modifiers: age, ISS stage, ECOG PS, cytogenetic risk, creatinine clearance and MM type. The ESS of the weighted IsaVRd population was 161 patients after matching, which is 61% of the original sample size (N = 265) suggesting reasonable population overlap (Table 38 in Appendix D.3.2).

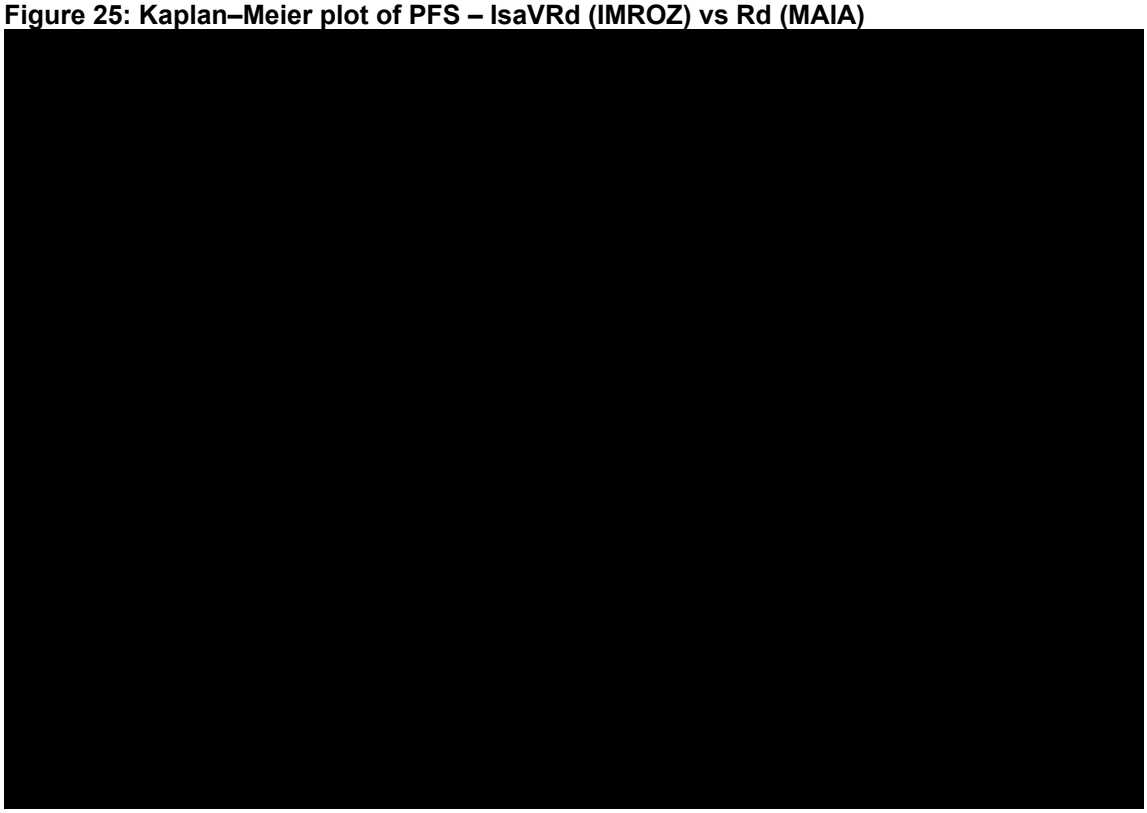
The patient baseline characteristics for IsaVRd and Rd before and after matching are provided in Appendix D.3.2.2.1. Patient populations with respect to the matching variables were well-balanced following adjustment.

Additional results for weight histograms, PH assessments, bootstrapped HRs, and weighted PSM model fit statistics are provided in Appendix D.3.2.2.9.

PFS

The MAIC of IsaVRd versus Rd suggests that the relative treatment effect between IsaVRd and Rd is slightly less when adjusting for differences in patient characteristics. This is shown by the smaller difference in the Kaplan–Meier curves (Figure 25).

Figure 25: Kaplan–Meier plot of PFS – IsaVRd (IMROZ) vs Rd (MAIA)



Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; ITC, indirect treatment comparison; PFS, progression-free survival; Rd, lenalidomide and dexamethasone.

Results from the standard MAIC, which estimate constant HRs, indicate that IsaVRd provides statistically significantly reduced hazard of progression or death compared with Rd (HR: [redacted] [95% CI; [redacted]]) (Table 27). Additional results are provided in Appendix D.3.2.

Table 27: Hazard ratios for PFS – IsaVRd (IMROZ) vs Rd (MAIA)

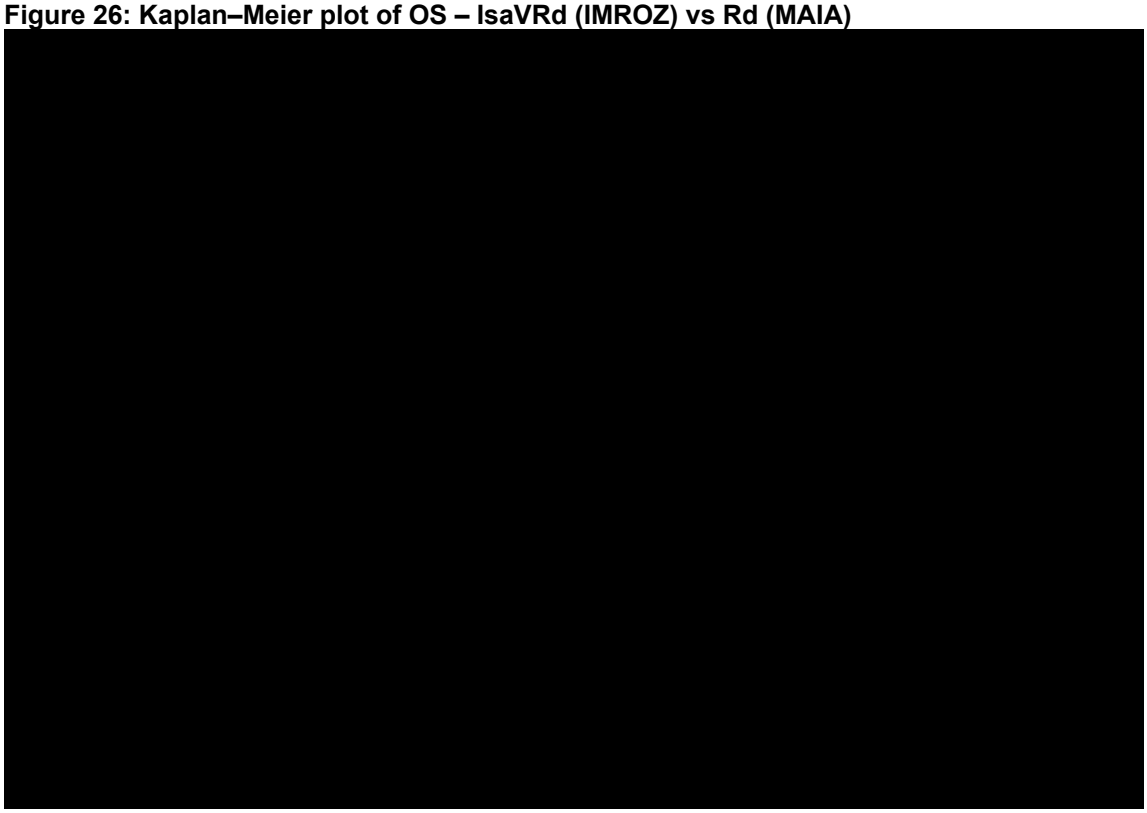
Method	HR (95% CI)
HR (95% CI) from unadjusted Cox model	[redacted]
HR (95% CI) from weighted Cox model	[redacted]
Bootstrap median HR (95% CI)	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; ITC, indirect treatment comparison; PFS, progression-free survival; Rd, lenalidomide and dexamethasone.
Notes: HR <1 favours IsaVRd. Results are considered statistically significant if 1 does not fall within the 95% CI. Bootstrapped HRs show an approximately normal distribution, so the 95% CI based on the 2.5th and 97.5th percentiles is considered reliable for estimating the uncertainty.

OS

The relative treatment effect between IsaVRd and Rd is reduced following adjustment as shown by the smaller difference in Kaplan–Meier curves (Figure 26).

Figure 26: Kaplan–Meier plot of OS – IsaVRd (IMROZ) vs Rd (MAIA)



Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; ITC, indirect treatment comparison; OS, overall survival; Rd, lenalidomide and dexamethasone.

Results from the standard MAIC, which estimates a constant HR, estimate an increased HR following adjustment (HR: [redacted] [95% CI; [redacted]]), suggesting IsaVRd provides a statistically significant lower hazard of death compared with Rd (Table 28). Additional results are provided in Appendix D.3.2.

Table 28: Hazard ratios for OS – IsaVRd (IMROZ) vs Rd (MAIA)

Method	HR (95% CI)
HR (95% CI) from unadjusted Cox model	[redacted]
HR (95% CI) from weighted Cox model	[redacted]
Bootstrap median HR (95% CI)	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; ITC, indirect treatment comparison; OS, overall survival; Rd, lenalidomide and dexamethasone.
Notes: HR <1 favours IsaVRd. Results are considered statistically significant if 1 does not fall within the 95% CI. Bootstrapped HRs show an approximate normal distribution, meaning the 95% CI based on the 2.5th and 97.5th percentiles is deemed a reliable method for estimating the uncertainty.

IsaVRd vs VMP (ALCYONE)

MAICs were conducted to estimate the comparative efficacy between IsaVRd and VMP using IMROZ and ALCYONE, respectively. Analyses were conducted using all available characteristics identified as potential prognostic factors or effect modifiers: age, ISS stage, ECOG PS, cytogenetic risk and MM type. The ESS of the weighted IsaVRd

population was 145 patients after matching, which was 55% of the original sample size (N = 265) (Table 39 in Appendix D.3.2).

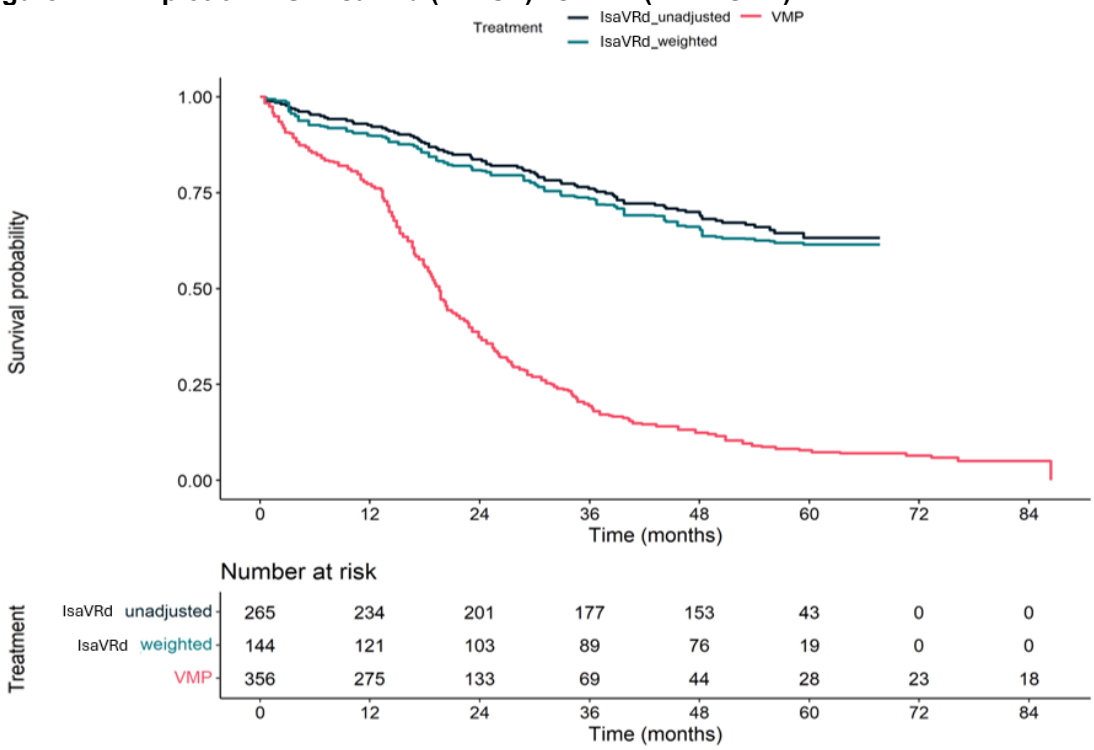
The patient baseline characteristics for IsaVRd and VMP before and after matching are provided in Appendix D.3.2.2.1. Patient populations with respect to the matching variables were well-balanced following adjustment.

Additional results for weight histograms, PH assessments, bootstrapped HRs, and weighted PSM model fit statistics are provided in Appendix D.3.2.2.9.

PFS

Following adjustment of patient characteristics, the relative treatment effect between IsaVRd and VMP is reduced, as shown by the smaller difference in the Kaplan–Meier curves (Figure 27).

Figure 27: KM plot of PFS – IsaVRd (IMROZ) vs VMP (ALCYONE)



Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; ITC, indirect treatment comparison; PFS, progression-free survival; VMP, bortezomib, melphalan and prednisone.

Results are provided in Table 29. For the standard MAIC, which estimates constant HRs, the HR increased from 0.18 (95% CI; 0.14, 0.23) in the unadjusted analysis to 0.20 (95% CI; 0.15, 0.26) using bootstrapping with percentile CI. Results indicate IsaVRd provides a statistically significantly lower hazard of progression or death compared with VMP. The sensitivity analyses using alternative methods to estimate the CI provided consistent results. Additional results are provided in Appendix D.3.2.

Table 29: Hazard ratios for PFS – IsaVRd (IMROZ) vs VMP (ALCYONE)

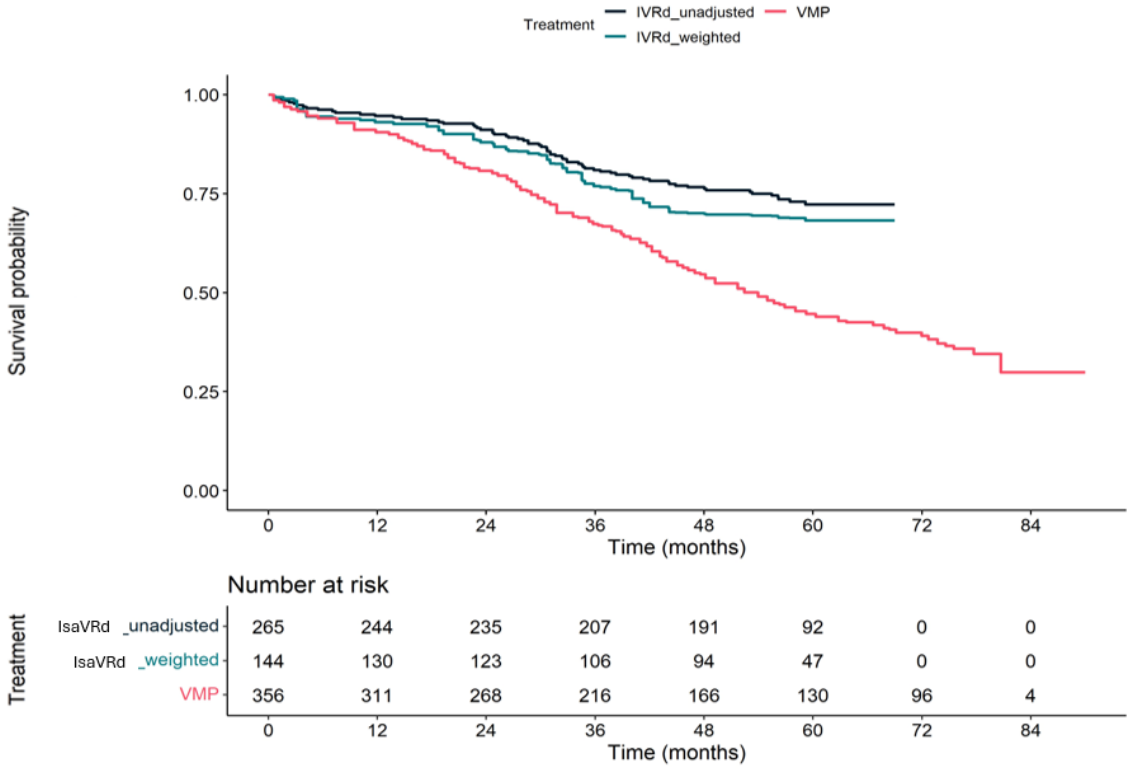
Method	Hazard ratio (95% CI)
HR (95% CI) from unadjusted Cox model	0.18 (0.14, 0.23)
HR (95% CI) from weighted Cox model	0.20 (0.15, 0.27)
Bootstrap median HR (95% CI)	0.20 (0.15, 0.26)

Abbreviations: CI, confidence interval; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; ITC, indirect treatment comparison; PFS, progression-free survival; VMP, bortezomib, melphalan and prednisone.
Notes: HR <1 favours IsaVRd. Results are considered statistically significant if 1 does not fall within the 95% CI. As the bootstrapped HRs show an approximately normal distribution, the 95% CI based on 2.5th and 97.5th percentiles is considered reliable for estimating the uncertainty.

OS

The relative treatment effect between IsaVRd and VMP is reduced following adjustment as shown by the Kaplan–Meier curves (Figure 28).

Figure 28: Kaplan–Meier plot of OS – IsaVRd (IMROZ) vs VMP (ALCYONE)



Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; ITC, indirect treatment comparison; OS, overall survival; VMP, bortezomib, melphalan and prednisone.

In the standard MAIC, which estimates a constant HR, the HR increased from 0.41 (95% CI; 0.31, 0.54) in the unadjusted analysis to 0.50 (95% CI; 0.37, 0.65) for the MAIC using bootstrapping with percentile CI, indicating IsaVRd provides a statistically significant lower hazard of death compared with VMP (Table 30). Additional results are provided in Appendix D.3.2.

Table 30: Hazard ratios for OS – IsaVRd (IMROZ) vs VMP (ALCYONE)

Method	HR (95% CI)
HR (95% CI) from unadjusted Cox model	0.41 (0.31, 0.54)
HR (95% CI) from weighted Cox model	0.50 (0.37, 0.67)
Bootstrap median HR (95% CI)	0.50 (0.37, 0.65)

Abbreviations: CI, confidence interval; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; ITC, indirect treatment comparison; OS, overall survival; VMP, bortezomib, melphalan and prednisone.
Notes: HR <1 favours IsaVRd. Results are considered statistically significant if 1 does not fall within the 95% CI. Highlight indicates the preferred model. As the bootstrapped HRs show an approximately normal distribution, the 95% CI based on the 2.5th and 97.5th percentiles is considered reliable for estimating the uncertainty.

IsaVRd vs VCd (Flatiron data source)

An IPW was conducted to provide data for comparing IsaVRd versus VCd. Analyses were conducted using all available characteristics identified as potential prognostic factors or effect modifiers: age, ECOG PS, ISS stage, time since diagnosis, cytogenetic risk and chromosomal abnormality 1q21+. The ESS of the weighted IsaVRd population was 123 patients after matching, which was 49% of the unadjusted Flatiron sample size (N = 249) (Table 59 in Appendix D.3.2).

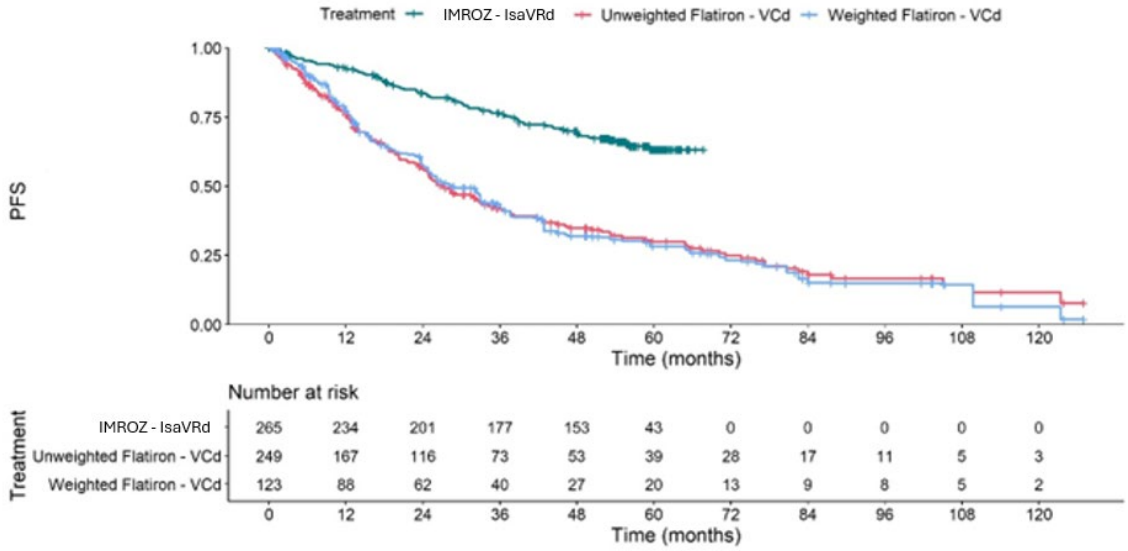
The patient baseline characteristics for IsaVRd and VCd before and after matching are provided in Appendix D.3.3. Patient populations with respect to the matching variables were well-balanced following adjustment.

Additional results for weight histograms, PH assessments, and weighted PSM model fit statistics are provided in Appendix D.3.2.2.9.

PFS

The PFS Kaplan–Meier curves for IsaVRd and VCd before and after matching using IPW analysis are presented in Figure 29. The adjustment for differences in patient characteristics had little impact on the PFS of patients treated with VCd.

Figure 29: Kaplan–Meier plot of PFS – IsaVRd (IMROZ) vs VCd (Flatiron data source)



Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; ITC, indirect treatment comparison; PFS, progression-free survival; VCd, bortezomib, cyclophosphamide and dexamethasone.

Following adjustment, results suggest that IsaVRd provides statistically significantly reduced hazard of progression or death compared with VCd (HR: 0.34 [95% CI; 0.25, 0.47]) (Table 31). Additional results are provided in Appendix D.3.2.

Table 31: Hazard ratios for PFS – IsaVRd (IMROZ) vs VCd (Flatiron data source)

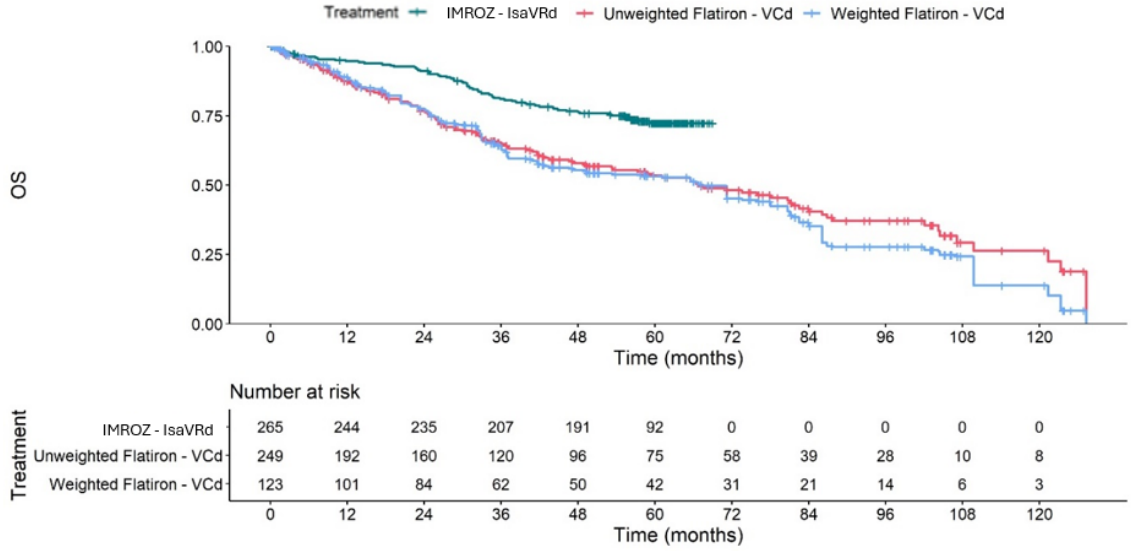
Method	Hazard ratio (95% CI)
HR (95% CI) from unweighted VCd	0.35 (0.27, 0.46)
HR (95% CI) from weighted VCd	0.34 (0.25, 0.47)

Abbreviations: CI, confidence interval; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; PFS, progression-free survival; VCd, bortezomib, cyclophosphamide, dexamethasone.

OS

The OS Kaplan–Meier curves for IsaVRd and VCd before and after matching using IPW analysis are presented in Figure 30.

Figure 30: Kaplan–Meier plot of OS – IsaVRd (IMROZ) vs VCd (Flatiron data source)



Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; ITC, indirect treatment comparison; OS, overall survival; VCd, bortezomib, cyclophosphamide and dexamethasone.

The adjustment for differences in patient characteristics had little impact on the OS of patients treated with VCd (Table 32). Following adjustment, results suggest that IsaVRd provides statistically significant reduced hazard of death compared with VCd (HR: 0.48 [95% CI; 0.33, 0.69]). Additional results are provided in Appendix D.3.2.

Table 32: Hazard ratios for OS – IsaVRd (IMROZ) vs VCd (Flatiron data source)

Method	Hazard ratio (95% CI)
HR (95% CI) from unweighted VCd	0.49 (0.36, 0.66)
HR (95% CI) from weighted VCd	0.48 (0.33, 0.69)

Abbreviations: CI, confidence interval; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; OS, overall survival; VCd, bortezomib, cyclophosphamide, dexamethasone.

B.2.9.4.2 Heterogeneity and inconsistency

A summary of heterogeneity between IMROZ and comparator sources is provided in Table 33.

Table 33: Summary of heterogeneity between IMROZ and comparator sources

Study/ data source	Comparisons supported	Median follow up (months)	Heterogeneity between comparator source and IMROZ
MAIA	DRd, Rd	73.6 (OS) 64.5 (PFS)	• Little variation in study design, inclusion/exclusion criteria, baseline characteristics and outcome data across trials
ALCYONE	VMP	78.8	• Little variation in study design, inclusion/exclusion criteria, baseline characteristics and outcome data across trials
FIRST	Rd	67	• Little variation in study design, inclusion/exclusion criteria, baseline characteristics and outcome data across trials
Flatiron data source	VCd	NR	• Eligibility for SCT was not captured in Flatiron. Therefore, patients who did not receive an ASCT were used as a proxy for the transplant-ineligible population • Flatiron was a US-based study whereas IMROZ was multicenter international • Retrospective study (Flatiron) versus prospective study (IMROZ)

Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; NR, not reported; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; SCT, stem-cell transplant; VCd, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

B.2.9.4.3 NMA

Standard PH NMA results

Model fit statistics for the standard NMA are provided in Appendix 3.1.7.

OS

The HRs estimated from the standard PH NMA for OS are provided in Table 34. Results of the NMA indicate IsaVRd provides a reduced hazard of death (HR <1) versus DRd, Rd, and VMP.

Table 34: HRs for IsaVRd versus each treatment – standard PH NMA (OS)

Treatment	HR (95% CrI)
DRd	[redacted]

Treatment	HR (95% CrI)
Rd	[redacted]
VMP	0.58 (0.32, 1.07)

Abbreviations: CrI, credible interval; DRd, daratumumab, lenalidomide, and dexamethasone; FE, fixed effects; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; NMA, network meta-analysis; OS, overall survival; PH, proportional hazard; Rd, lenalidomide and dexamethasone; VMP, bortezomib, melphalan and prednisone.
Notes: HR <1 indicates reduced hazard of death for IsaVRd.

The OS HRs for each treatment vs VRd estimated from the standard PH NMA are provided in Appendix D.3.1.7.

PFS

The PFS HRs for IsaVRd vs each treatment estimated from the standard PH NMA are provided in Table 35. A HR <1 indicates a reduced hazard of progression or death for IsaVRd. The results indicate that IsaVRd provides reduced hazard of progression or death (HR <1) vs DRd, Rd and VMP. Results suggest IsaVRd provides a numerical reduction in the hazard of progression of death compared with DRd (HR: [redacted] [95% CrI; [redacted]]), although results are not statistically significant. Comparisons versus all other treatments (except DRd) are statistically significant as the 95% CrIs do not include 1.

Table 35: HRs for IsaVRd versus each treatment – standard PH NMA (PFS)

Treatment	HR (95% CrI)
DRd	[redacted]
Rd	[redacted]
VMP	0.44 (0.26, 0.76)

Abbreviations: CrI, credible interval; DRd, daratumumab, lenalidomide, and dexamethasone; FE, fixed effects; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; NMA, network meta-analysis; PFS, progression-free survival; RE, random effects; Rd, lenalidomide and dexamethasone; VMP, bortezomib, melphalan, and prednisone.
Notes: HR <1 indicates reduced hazard of death for IsaVRd; highlighted indicates statistically significant results.

The PFS HRs for each treatment vs VRd estimated from the standard PH NMA are provided in Appendix D.3.1.7.

Comparison of MAIC and standard NMA for the comparison vs DRd

A comparison of results from the standard NMA and MAIC for IsaVRd vs DRd is presented in Table 36. Results for OS suggest a similar and reduced hazard of death for IsaVRd vs DRd in the NMA and MAIC, however results are not statistically significant. Results from the standard NMA suggest a reduced hazard of progression or death for IsaVRd vs DRd compared with the MAIC. However, only the MAIC is statistically significant. This consistency in direction across both analyses supports the benefit of IsaVRd over DRd in terms of OS.

Table 36: IsaVRd vs DRd - Comparison of results for standard NMA and MAIC – OS and PFS

	Standard NMA (FE)	MAIC
	HR (95% CrI)	HR (95% CI)
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CrI, credible interval; DRd, daratumumab, lenalidomide, and dexamethasone; FE, fixed effects; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; MAIC, matching adjusted indirect comparisons; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival.

Conclusion

Unanchored MAIC was deemed the most suitable approach to assess comparative efficacy vs DRd, Rd, and VMP, as well as an IPW for the VCd comparison. The MAICs and IPW showed evidence that IsaVRd provides statistically significant improvements in PFS and OS compared with all other comparators, except for OS when compared with DRd. A standard NMA was also conducted as an alternative using stratified HRs reported for PFS and OS from SWOG-S0777, and the results support a benefit of IsaVRd vs DRd in terms of OS, even if not statistically significant.

A key strength of population-adjusted analyses is the ability to adjust for observed differences in patient characteristics, allowing outcomes to be compared across balanced trial populations. As an example, IMROZ excluded patients over 80 years old that were not excluded in other clinical trials.

Furthermore, the use of MAIC avoided the need to rely on several limiting assumptions in the connected network of evidence for NMA. The limitations of the network were primarily related to the inclusion of a non-randomised subgroup from the SWOG S0777 trial, used as a proxy for the TI population. This introduced substantial bias due to imbalances in patient characteristics and the lack of specific outcome data for the TI subgroup. The reported stratified HRs for OS and PFS in SWOG-S0777 did not include age as a stratification factor. Consequently, residual confounding may exist, as the stratified analysis might not fully account for the influence of age on treatment effects.

Additionally, differences in patient populations, such as the inclusion of a meaningful proportion of patients with an intent to transplant in the subgroup of those aged ≥ 65 years in SWOG-S0777, and confounding factors related to the early discontinuation in the induction VRd arm due to the IV administration of bortezomib, further complicated the interpretation.

Another strength of the MAIC is its ability to estimate time-varying relative effects that relax the PH assumption. In this case, the PH assumption does not hold for PFS and OS in the NMA network as described in Appendix 3.1.7, and a method that allows for a time-varying approach would be more appropriate. A parametric NMA was not considered appropriate due do the lack of randomisation. In addition to limitations previously described, using Kaplan-Meier curves from a non-randomised subgroup may result both unreliable HR and incorrect direction of the treatment effect over time. A parametric MAIC was deemed the best option to reliably estimate HRs and the direction of the treatment effect for extrapolation in the cost-effectiveness analysis. OS and PFS extrapolations are further described in B.3.3.

B.2.10 *Adverse reactions*

The addition of isatuximab to VRd was associated with a manageable tolerability profile

- Although the percentage of patients with Grade ≥3 TEAEs was higher in the IsaVRd group (91.6%) compared with the VRd group (84.0%)
  - Once adjusted for exposure, little difference was observed (1.171 and 0.986 events per patient-year, respectively)
- Grade 5 TEAEs were reported for 29 (11.0%) participants in the IsaVRd group and 10 (5.5%) participants in the VRd group
  - This difference was largely driven by the difference in treatment exposure (exposure-adjusted rates for Grade 5 TEAEs are 0.031 and 0.019 events per patient year with IsaVRd and VRd, respectively)
- IMROZ was conducted during the COVID-19 pandemic; in total, eight of the fatal TEAEs in the IsaVRd arm were related to COVID-19 compared with two in the VRd arm
- The proportion of patients experiencing treatment-emergent serious adverse events (SAEs) (70.7% and 67.4%, respectively) and TEAEs leading to definitive treatment discontinuation were similar between IsaVRd and VRd (22.8% and 26.0%, respectively)
- Infusion reactions (IRs) of any grade were reported in 63 (24.0%) participants in the IsaVRd group
  - All were Grade 1 or 2 except one participant who had a Grade 3 IR and another one who had a Grade 4 anaphylactic reaction
- Second primary malignancies were reported in 42 (16.0%) and 16 (8.8%) participants in the IsaVRd and VRd groups, respectively
  - The exposure-adjusted incidence rates were 0.041 and 0.026 events per patient year in the IsaVRd and VRd groups, respectively
- The median relative dose intensities (RDIs) were similar in the IsaVRd and VRd groups for bortezomib (90.28% vs 86.65%, respectively), lenalidomide (77.74% vs 83.45%, respectively) and for dexamethasone (81.58% vs 79.34%)
  - The median RDI of isatuximab was 93.58%

B.2.10.1 *Studies included*

Safety evidence for IsaVRd in the population of interest for this submission is provided by the IMROZ study.

B.2.10.1.1 Adverse events

The percentage of participants with Grade ≥3 TEAEs was higher in the IsaVRd group (91.6%) compared with the VRd group (84.0%) (Table 37). However, once adjusted for exposure, the rates were similar (1.171 and 0.986 event per patient-year, respectively).

Grade 5 TEAEs were reported for 29 (11.0%) participants in the IsaVRd group and 10 (5.5%) participants in the VRd group. This difference was largely driven by the

difference in treatment exposure (exposure-adjusted rates for Grade 5 TEAEs are 0.031 and 0.019 events per patient year with IsaVRd and VRd, respectively).

Table 37: Patient years analysis: overview of TEAEs – Safety population

	IsaVRd (N=263)		VRd (N=181)	
	n (%)	Event rate per patient year†	n (%)	Event rate per patient year†
Patients with any TEAE	262 (99.6)	13.386	178 (98.3)	12.691
Patients with any Grade ≥3 TEAE	241 (91.6)	1.171	152 (84.0)	0.986
Patients with any Grade 5 TEAE	29 (11.0)	0.031	10 (5.5)	0.019
Patients with any TEAE leading to definitive treatment discontinuation	60 (22.8)	0.066	47 (26.0)	0.090
Serious TEAEs		0.37		0.43

Abbreviations: CSR, clinical study report; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone combination; SAE, serious adverse events; TEAE, treatment-emergent adverse event; VRd, bortezomib, lenalidomide, and dexamethasone combination.
Source: IMROZ CSR, 2024 (88).

A summary of haematologic laboratory abnormalities and common AEs is provided in Table 38 (76).

Table 38: Summary of haematologic laboratory abnormalities, adverse events of any grade, and second primary cancers (Safety Population)

Event†	IsaVRd (N=263)		VRd (N=181)	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Haematologic laboratory abnormalities‡				
Anaemia	260 (98.9)	46 (17.5)	177 (97.8)	29 (16.0)
Lymphopenia	251 (95.4)	158 (60.1)	167 (92.3)	96 (53.0)
Neutropenia	230 (87.5)	143 (54.4)	145 (80.1)	67 (37.0)
Leukopenia	256 (97.3)	83 (31.6)	160 (88.4)	30 (16.6)
Thrombocytopenia	251 (95.4)	79 (30.0)	153 (84.5)	50 (27.6)
Nonhaematologic adverse events				
Infection§	240 (91.3)	118 (44.9)	157 (86.7)	69 (38.1)
Pneumonia	79 (30.0)	53 (20.2)	35 (19.3)	23 (12.7)
Bronchitis	58 (22.1)	7 (2.7)	32 (17.7)	3 (1.7)
Upper respiratory tract infection	90 (34.2)	2 (0.8)	61 (33.7)	2 (1.1)
Diarrhoea	144 (54.8)	20 (7.6)	88 (48.6)	15 (8.3)
Peripheral sensory neuropathy	143 (54.4)	19 (7.2)	110 (60.8)	11 (6.1)

Event†	IsaVRd (N=263)		VRd (N=181)	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Cataract	100 (38.0)	41 (15.6)	46 (25.4)	20 (11.0)
Constipation	94 (35.7)	6 (2.3)	74 (40.9)	3 (1.7)
Fatigue	91 (34.6)	21 (8.0)	48 (26.5)	12 (6.6)
Peripheral oedema	86 (32.7)	0	59 (32.6)	2 (1.1)
Infusion-related reaction	62 (23.6)	1 (0.4)	2 (1.1)	0
Covid-19¶	78 (29.7)	23 (8.7)	37 (20.4)	12 (6.6)
Insomnia	59 (22.4)	10 (3.8)	44 (24.3)	4 (2.2)
Back pain	58 (22.1)	9 (3.4)	31 (17.1)	3 (1.7)
Asthenia	57 (21.7)	7 (2.7)	44 (24.3)	4 (2.2)
Invasive second primary cancer††				
Solid tumour‡‡	22 (8.4)	14 (5.3)	8 (4.4)	6 (3.3)
Haematologic cancer	3 (1.1)	1 (0.4)	2 (1.1)	2 (1.1)
Event rate per patient-year§§				
Infections	1.181	0.174	1.166	0.171
Second primary malignancies¶¶	0.041		0.026	

Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone combination; MedDRA, Medical Dictionary for Regulatory Activities; VRd, bortezomib, lenalidomide, and dexamethasone.
† The safety population included all the patients who received at least one dose of trial treatment. Source: Facon et al., 2024 (76); Manier et al., 2024 (95).

B.2.10.1.2 Serious adverse events

The percentages of patients experiencing treatment-emergent serious adverse events (SAEs) were similar with IsaVRd and VRd (70.7% and 67.4%, respectively) (Table 39). Overall, the exposure-adjusted incidence of treatment-emergent SAEs was similar between the IsaVRd and VRd groups (0.375 and 0.435). When exposure adjusted incidence was compared at the SOC level, treatment-emergent SAEs occurred at a similar frequently in the IsaVRd and VRd groups.

The most frequently reported serious TEAEs (≥10% of participants in either group) (all grades, regardless of causal relationship) are provided in Table 39.

Table 39: Patient years analysis: overview of SAEs – Safety population

	IsaVRd (N=263)		VRd (N=181)	
	n (%)	Event rate per patient year†	n (%)	Event rate per patient year†
Patients with any treatment emergent SAE	186 (70.7)	0.375	122 (67.4)	0.435
Infections and infestations	116 (44.1)	0.173	66 (36.5)	0.165

	IsaVRd (N=263)		VRd (N=181)	
Nervous system disorders	24 (9.1)	0.028	23 (12.7)	0.047

Abbreviations: CSR, clinical study report; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; SAE, serious adverse events; VRd, bortezomib, lenalidomide, and dexamethasone.
n (%) = number and percentage of patients with at least one TEAE.
† Calculated as number of patients with an event divided by total patient years.
Source: IMROZ CSR, 2024 (88).

B.2.10.1.3 Exposure

The median duration of exposure was 53.16 months (range 0.5 to 68.8) in the IsaVRd group and 31.28 months (range 0.6 to 67.2) in the VRd group. The median number of cycles started was 52.00 (range 1 to 69) in the IsaVRd group and 29.00 (range 1 to 69) in the VRd group.

The median RDIs were similar in the IsaVRd and VRd groups for bortezomib (90.28% vs 86.65%, respectively), lenalidomide (77.74% vs 83.45%, respectively) and for dexamethasone (81.58% vs 79.34%). The median RDI of isatuximab was 93.58%. A comparison of the exposure for the components of the IsaVRd treatment regimen are provided in Table 40.

Table 40: Comparative table of exposure for components of IsaVRd

	Isatuximab	Bortezomib		Lenalidomide		Dexamethasone	
	IsaVRd	IsaVRd	VRd	IsaVRd	VRd	IsaVRd	VRd
Relative dose intensity (%)							
Mean (SD)	92.19 (10.26)	86.05 (16.12)	84.74 (17.59)	76.98 (31.05)	79.41 (29.00)	21.38 (12.32)	24.74 (13.22)
Median	93.58	90.28	86.65	77.74	83.45	20.09	21.45
Median duration of exposure (months)	53.16	5.52	5.52	46.13	31.28	46.69	20.34

Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; SD, standard deviation; VRd, bortezomib, lenalidomide, and dexamethasone.

B.2.10.1.4 Discontinuations and/or dose modifications due to adverse events

Treatment discontinuation

Definitive treatment discontinuation was defined as discontinuation of all study intervention or the last ongoing study drug.

Overall, 60 (22.8%) and 47 (26.0%) participants in the IsaVRd and VRd groups, respectively, had TEAEs leading to definitive treatment discontinuation. Definitive treatment discontinuation was most frequently due to COVID-19 pneumonia (8 [3.0%]) in the IsaVRd group. A summary of the proportions of patients who had TEAEs leading to premature discontinuations is provided in Table 41.

Table 41: Overview of Treatment-Emergent Adverse Events (TEAEs) – Safety population

	IsaVRd (N=263)	VRd (N=181)
Patients with any TEAE leading to definitive treatment discontinuation [n (%)]	60 (22.8)	47 (26.0)
Patients with any TEAE leading to premature discontinuation of isatuximab [n (%)]	6 (2.3)	NA
Patients with any TEAE leading to premature discontinuation of bortezomib [n (%)]	32 (12.2)	17 (9.4)
Patients with any TEAE leading to premature discontinuation of lenalidomide [n (%)]	34 (12.9)	4 (2.2)
Patients with any TEAE leading to premature discontinuation of dexamethasone [n (%)]	18 (6.8)	31 (17.1)

Abbreviations: CSR, clinical study report; IR, infusion reaction; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; NA, not applicable; TEAE, treatment-emergent adverse events; VRd, bortezomib, lenalidomide, and dexamethasone.
n (%) = Number and percentage of patients with at least one TEAE.
Source: IMROZ CSR, 2024 (88).

Adverse events leading to dose delay

Overall, 191 (72.6%) participants in the IsaVRd group and 117 (64.6%) participants in the VRd group had at least 1 TEAE (all grades) leading to dose delay, the most frequent of which were: neutropenia (58 [22.1%] vs 33 [18.2%] participants in the IsaVRd and VRd group, respectively), COVID-19 (40 [15.2%] vs 16 [8.8%], respectively), upper respiratory tract infection (31 [11.8%] vs 16 [8.8%], respectively), and pneumonia (42 [16.0%] vs 12 [6.6%], respectively).

Adverse events leading to dose interruption or dose omission of isatuximab

An isatuximab dose interruption was defined as an infusion administration that was stopped during an infusion before it was completed, regardless of whether it was further restarted or not. Treatment-emergent AEs leading to dose interruption were reported in 56 (21.3%) participants in the IsaVRd group, the most frequent of which was infusion-related reaction (55 [20.9%] participants). No participants experienced TEAEs of Grade ≥3 that led to dose interruptions.

Adverse events leading to dose reduction

Dose reductions and omissions were permitted for lenalidomide, bortezomib, and dexamethasone. Dose reductions were not permitted for isatuximab, but dose omissions were permitted. "Dose reduction" was recorded as the action taken for both dose reductions and dose omissions.

Isatuximab dose omission

Treatment-emergent AEs led to isatuximab dose reductions/omissions in 137 (52.1%) participants in the IsaVRd group. The most frequently reported TEAE leading to dose reduction (with an incidence ≥10%) was upper respiratory tract infection.

Bortezomib dose reduction or omission

Treatment-emergent AEs led to bortezomib dose reductions/omissions in 183 (69.6%) participants in the IsaVRd group and 127 (70.2%) participants in the VRd group. The most frequently reported TEAE leading to dose reduction (with an incidence ≥10% in either group) was peripheral sensory neuropathy (74 [28.1%] in the IsaVRd group and 55 [30.4%] in the VRd group).

Lenalidomide dose reduction or omission

Treatment-emergent AEs led to lenalidomide dose reductions/omissions in 218 (82.9%) participants in the IsaVRd group and 141 (77.9%) participants in the VRd group. The most frequently reported TEAEs leading to dose reduction (with an incidence ≥10% in either group) were diarrhoea (38 [14.4%] in the IsaVRd group and 23 [12.7%] in the VRd group), neutropenia (49 [18.6%] and 21 [11.6%], respectively), pneumonia (27 [10.3%] and 18 [9.9%], respectively) and upper respiratory tract infection (29 [11.0%] and 17 [9.4%], respectively).

Dexamethasone dose reduction or omission

Treatment-emergent AEs led to dexamethasone dose reductions/omissions in 216 (82.1%) participants in the IsaVRd group and 140 (77.3%) participants in the VRd group. The most frequently reported TEAEs leading to dose reduction (with an incidence ≥10% in either group) were pneumonia (32 [12.2%] in the IsaVRd group and 17 [9.4%] in the VRd group) and upper respiratory tract infection (28 [10.6%] and 13 [7.2%], respectively).

B.2.10.2 *Additional studies*

B.2.10.2.1 BENEFIT (NCT04751877)

The Phase III BENEFIT study was the first academic, French trial conducted to demonstrate the efficacy and safety profile of IsaVRd, using weekly bortezomib (V) and reduced, fixed-dose dexamethasone, compared with the triplet combination IsaRd in a population of TI patients with NDMM.

A total of 270 patients were enrolled with 135 assigned to each arm. Patients received at least one dose of treatment. The baseline characteristics were well balanced across the treatment arms.

At a median follow-up of 23.5 months, the most common AEs (occurring in ≥10% of patients in either group) were as follows:

- Neutropenia (56% in IsaVRd vs 61% in IsaRd)
- Diarrhoea (48% in both arms)
- Infection (47% in IsaVRd vs 39% in IsaRd)

The BENEFIT study was identified via hand searching of recent conference proceedings and the clinicaltrials.gov website. This study is not considered relevant due to differences in the trial design, including the population of interest and the primary endpoint (MRD rate). Therefore, this study cannot be used to infer comparisons with IMROZ. Additionally, no results from the BENEFIT study will be included in the label.

B.2.11 *Ongoing studies*

IMROZ (refer to Section B.2) is ongoing and is expected to complete in 2027. An additional data cut is expected in Q1/Q2 of 2025. The data presented in Section B.2 are from the latest data cut (26 September 2023).

B.2.12 *Interpretation of clinical effectiveness and safety evidence*

B.2.12.1 *Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology*

The results of the Phase III, international, prospective, randomised, open-label IMROZ clinical trial demonstrated that IsaVRd is a more effective treatment option than VRd as initial therapy in adult TI patients with NDMM at a median follow-up of 59.73 months (88). Following treatment with IsaVRd and VRd, 31.7% and 43.1% of patients respectively, experienced death or disease progression. At 60 months, the PFS was 63.2% in the IsaVRd group compared with 45.2% in the VRd group, demonstrating the profound PFS benefit with the IsaVRd regimen vs the VRd regimen. The HR for death or disease progression was 0.596 (98.5% CI; 0.406, 0.876), which corresponds to a reduction of 40.4% in risk of disease progression or death for IsaVRd vs VRd.

Secondary and other key efficacy endpoints also demonstrate the clinical benefit to the addition of isatuximab to a VRd regimen. In patients who were treated with IsaVRd, a statistically significantly higher proportion achieved CR compared with VRd (74.7% vs 64.1%, respectively; p=0.008). There was a statistically significant improvement in the MRD-negative status in patients with a CR at any time in the IsaVRd group compared with the VRd group (55.5% vs 40.9% in ITT analysis, respectively; p=0.0013), as well as an improvement in the sustained MRD-negative status for more than 12 month (46.8% vs 24.3% respectively). The depth of response (“VGPR or better”) was enhanced in the IsaVRd group compared with the VRd group (89.1% vs 82.9%, respectively). The addition of isatuximab to VRd showed a favourable trend in OS for IsaVRd compared with VRd (HR: 0.776; [99.97% CI; 0.407, 1.480]; p=0.076); median OS was not reached in either group.

Subgroup analyses for the majority of the prespecified subgroups, including poor prognosis subgroups, showed a positive treatment effect favouring IsaVRd over VRd, consistent with the overall PFS analysis.

The IsaVRd regimen was associated with the known and manageable tolerability profile of each individual component of the regimen. Although the percentage of patients with Grade ≥3 TEAEs was higher in the IsaVRd group (91.6%) compared with the VRd group (84.0%), once adjusted for exposure, little difference was observed (1.171 and 0.986 event per patient-year, respectively). The percentages of patients experiencing treatment-emergent SAEs (70.7% and 67.4%, respectively) and TEAEs leading to definitive treatment discontinuation (22.8% and 26.0%, respectively) were similar with IsaVRd and VRd.

Since there were no direct head-to-head clinical trials with comparator treatments, indirect treatment comparisons were conducted and indicated that IsaVRd offers

statistically significant improvement in progression-free survival (PFS) compared with DRd, VMP, Rd, and VCd. Specifically, the constant HRs from matching-adjusted indirect comparisons (MAICs) were [redacted] (95% CI; [redacted], [redacted]) for IsaVRd vs DRd, [redacted] (95% CI; [redacted], [redacted]) for IsaVRd vs Rd, and 0.20 (95% CI; 0.15, 0.26) for IsaVRd vs VMP. The HR from inverse probability weighting (IPW) results showed a statistically significant improvement in PFS for IsaVRd vs VCd with a HR of 0.34 (95% CI; 0.25, 0.47). For OS, a MAIC analysis comparing IsaVRd vs DRd showed a trend towards improvement with a HR of [redacted] (95% CI; [redacted], [redacted]). Statistically significant improvements in OS were observed in MAICs comparing IsaVRd vs Rd with a HR of [redacted] (95% CI; [redacted], [redacted]) and IsaVRd vs VMP with a HR of 0.50 (95% CI; 0.37, 0.65). An IPW analysis comparing IsaVRd vs VCd showed a statistically significant improvement in OS with a HR of 0.48 (95% CI; 0.33, 0.69).

Based on IMROZ and the ITC HRs, IsaVRd is a superior first-line treatment option compared with DRd for selected adult patients with NDMM who are ineligible for transplant. It offers greater efficacy and maintains the known manageable safety profile of each individual component of the regimen. Additionally, the use of quadruplet therapy during the induction phase, followed by triplet therapy, suggests that IsaVRd and DRd have comparable side effect profiles.

B.2.12.2 *Strengths and limitations of the clinical evidence base for the technology*

B.2.12.2.1 Strengths of the evidence base

The clinical evidence base for IsaVRd includes a patient population that is consistent with that of the final scope.

IMROZ is a randomised clinical trial, with long median follow-up (59.73 months) and outcomes (PFS, OS, TTD, HRQoL, and AE) that are directly available to populate the economic model when collected.

The study population at enrolment was well balanced between the two treatment arms, with respect to the baseline disease characteristics.

Most of the patients in the IMROZ trial were from Europe, so the population does not differ fundamentally from the population with TI NDMM in the UK. Differences in relation to subsequent treatments have been adjusted for and do not impact overall survival for IsaVRd (Section B.2.6.1.3)

B.2.12.2.2 Potential limitations

In IMROZ, IsaVRd was compared with VRd which is not currently reimbursed in current NHS clinical practice. Head-to-head data were therefore not available for comparators in scope for this submission and necessitated indirect treatment comparisons.

Relative efficacy of IsaVRd versus comparators cannot be reliably estimated through a NMA due to the use of a non-randomised subgroup from the SWOG S0777 trial, used as a proxy for the TI population to allow network connectivity. Therefore, MAICs were conducted versus DRd, Rd, and VMP. Relative efficacy versus VCd was estimated using IPW.

The fact that the trial included a crossover treatment period can be considered a limitation. However, the cross-over design in IMROZ only impacted the VRd OS curve which is not a relevant comparator in the UK. Additionally, it does not affect the relative efficacy of IsaVRd vs comparators as MAICs and IPW were used in the base-case of the economic analysis. Regarding other subsequent treatments observed in IMROZ and not available in the NHS clinical practice, the IsaVRd OS curve showed no difference after adjustment, reducing the uncertainty on treatment effect.

B.3. Cost-effectiveness

Summary

- A 3-state partitioned survival model was developed to evaluate the cost-effectiveness of IsaVRd as a treatment for adult patients with newly diagnosed active multiple myeloma who are ineligible for ASCT
- The model took the form of a cost-utility analysis from the perspective of the NHS and Personal Social Services in England with a lifetime horizon of 29 years
- The base case compared IsaVRd with DRd as the main comparator, using the IMROZ clinical trial as the source of clinical characteristics
- The base case deterministic ICERs for IsaVRd vs DRd indicate that at list prices, IsaVRd dominates.
- Probabilistic sensitivity analyses provide results that are largely consistent with the base case, but show variability in incremental costs and ICER values

B.3.1 *Published cost-effectiveness studies*

B.3.1.1 *Identification of studies*

An SLR was conducted (finalised in January 2023) to identify the characteristics and results of economic models used to assess the cost-effectiveness of treatments for patients with NDMM. This report was updated on 29 April 2024.

Electronic databases were searched on 14 November 2022 and updated on 29 April 2024 via the OvidSP platform to identify peer-reviewed studies of interest. The databases searched included:

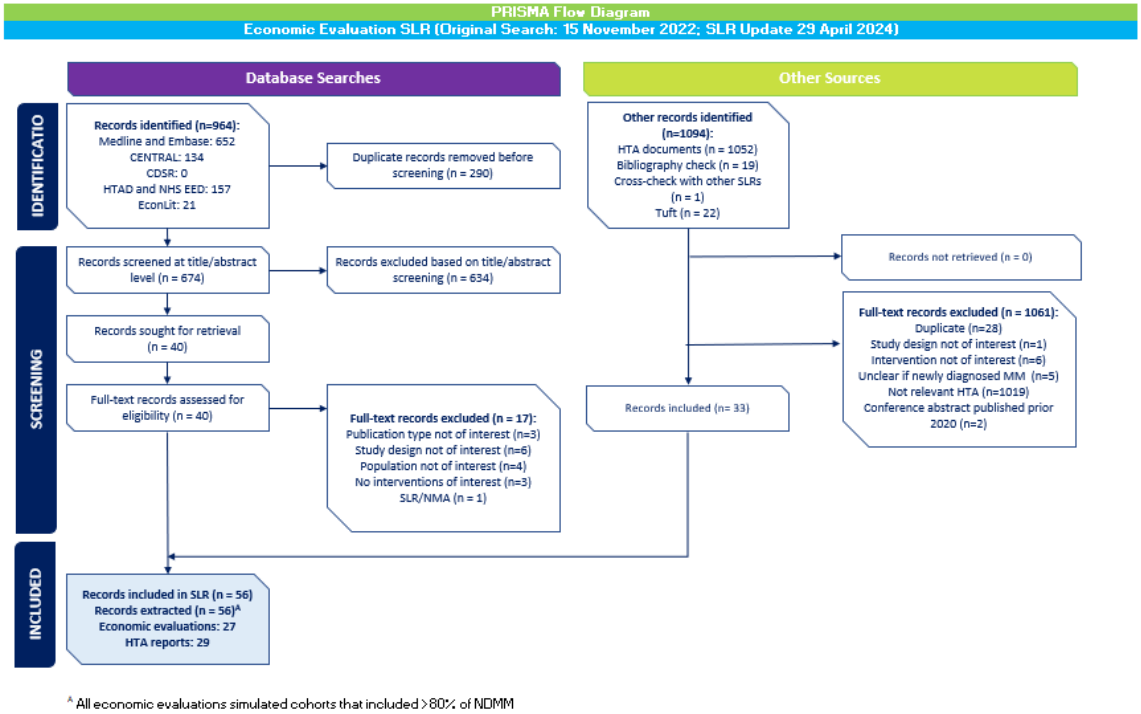
- Embase
- MEDLINE and MEDLINE In-Process
- EconLit
- CENTRAL
- Cochrane Database of Systematic reviews
- HTA Database
- National Health Service Economic Evaluation Database

Additional searches were conducted in conference proceedings, HTA websites and databases, and bibliographies of relevant SLRs published since 2016 to identify any publication not identified in the electronic database search phase. Full details of the searches and results for economic evaluation studies identified are reported in Appendix G.

The review identified 56 publications reporting on adult patients with NDMM. Of these, 27 were identified via database and grey literature searches; one was from the UK. The remaining 29 publications were reports identified through HTA bodies; six of these were from the UK. For full details, refer to Appendix G.

The PRISMA flow diagram for the April 2024 update is presented in Figure 31.

Figure 31: PRISMA diagram for economic evaluations (April 2024)



Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; HTA, health technology assessment; HTAD, Health Technology Assessment Database; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; NHS EED, National Health Service Economic Evaluation Database; NMA, network meta-analyses; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; SLR, systematic literature review.
Source: Economic and Humanistic SLR update (106).

B.3.1.2 *Description of identified studies*

Twenty-eight economic model publications reported results for a TI population; of these, one publication identified through database searches included the UK setting (as well as the EU4 [France, Germany, Italy, and Spain]), and three were models assessed by NICE (Table 42).

Table 42: Summary list of other cost-effectiveness evaluations

Study, Year, Country	Summary of model	Intervention/ comparator	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE TA917 2023 (72)	Cost utility analysis	DRd/ (i) Ld (ii) VCd (iii) VMP (iv) MPT (v) CTd	Untreated MM when stem cell transplant is unsuitable (not publicly available)	Not publicly available	Not publicly available	Not publicly available
NICE TA587, 2019 (73)	Cost utility analysis	Rd/MPT	First-line treatment of MM (not publicly available)	Not publicly available	Not publicly available	Not publicly available
NICE TA228, 2011 (71)	Cost utility analysis	Celgene model: MP and VMP/melphalan and MP Janssen and Assessment Group models: MPT; CTDa and VMP/MP	Newly diagnosed MM (not publicly available)	Not publicly available	Not publicly available	Not publicly available
Schey, 2017 (107) EU5	Cost impact analysis†	Thalidomide/ bortezomib, lenalidomide	Newly diagnosed MM (NR)	NA	Future Scenario A: additional expenditure of €867 per patient in Year 1, increasing to €3,358 per patient by Year 5	NA

Abbreviations: BCd, bortezomib, cyclophosphamide, and dexamethasone; BMP, bortezomib, melphalan, and prednisolone; CTDa, thalidomide, cyclophosphamide, and attenuated dexamethasone; DRd, daratumumab, lenalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; Ld, lenalidomide and dexamethasone; MM, multiple myeloma; MP, melphalan and prednisone; MPT, melphalan, prednisone with thalidomide; NA, not applicable; NR, not reported; QALY(s), quality-adjusted life year(s); Rd, lenalidomide and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

B.3.1.3 *Quality assessment of identified studies*

A quality assessment for the identified relevant studies is provided in Appendix G.3.

B.3.2 *Economic analysis*

From the economic SLR within the transplant ineligible studies, partitioned survival models (12/28), Markov and semi-Markov models (10/28) were by far the most

commonly used. Desk research was also conducted to consider appraisals in MM published post January 2023 by NICE, SMC, and CDA, which identified two appraisals that considered NDMM, both of which were appraisals for DRd (for NICE (33) and SMC (108)) and used a 3-state partitioned survival model (109-111). Partitioned survival models were also used in the NICE TAs of Rd and bortezomib-based regimens. Therefore, a 3-state partitioned survival model was chosen for this economic model. A summary of the base-case modelling framework is provided in Table 43.

Table 43. Base-case modelling framework

Population	Newly-diagnosed multiple myeloma (NDMM) patients who are ineligible for a stem cell transplant
Intervention	Isatuximab (Sarclisa®) in combination with bortezomib, lenalidomide and dexamethasone (IsaVRd)
Comparators	• Daratumumab, lenalidomide, and dexamethasone (DRd) • Lenalidomide and dexamethasone (Rd) • Bortezomib, cyclophosphamide, and dexamethasone (VCd) • Bortezomib, melphalan, and prednisone (VMP)
Analysis type	Cost-utility analysis
Perspective	NHS and Personal Social Services in England
Discount rate	3.5% for costs and QALYs
Model type	3-health state partitioned survival model
Health states	• Progression-free state (PF) • Post-progression state (PP) • Death
Cycle length	2 weeks (14 days)
Time horizon	Lifetime (29 years)
Currency	GBP 2023
Decision rule	WTP threshold of £20,000 to £30,000 per QALY

Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; NDMM, newly-diagnosed multiple myeloma; NHS, National Health Service; PF, progression-free state; PP, post-progression state; QALY, quality-adjusted life year; Rd, lenalidomide and dexamethasone; VCD, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone; WTP, willingness-to-pay.

B.3.2.1 *Patient population*

In line with the proposed licence and the IMROZ trial population, the cost-effectiveness model evaluates isatuximab (I) in combination with bortezomib (V), lenalidomide (R), and dexamethasone (d) for TI patients with NDMM patients using data from the ITT population of the IMROZ trial (Table 44).

Within the cost-effectiveness model, baseline patient characteristics are used to inform dosage derivation based on weight or body surface area (BSA) for some treatments and lenalidomide dosing based on renal impairment. Additionally, age and proportion of males are used for general population mortality.

Table 44: Mean patient characteristics

Characteristic	IMROZ (n=446*)	(SD)
Age at the start of the model	71.63	4.35
Proportion male	53%	NR
Average patient weight	73.58 kg	15.54 kg
Average body surface area	1.8 m^2	0.22 m^2
Proportion with regular renal function	70.9%	NR
Proportion with moderate renal impairment	29.1%	NR

Abbreviations: NR, not reported; SD, standard deviation.
Notes: *The intention-to-treat population was 446 patients, whereas the safety population was 444.
Source: IMROZ CSR, 2024 (88).

B.3.2.2 *Model structure*

A 3-state partitioned survival model (PSM) was chosen for this economic model, aligning directly with the primary and key secondary endpoints of the IMROZ trial (PFS and OS). The PSM approach offers several advantages, including ease of construction and the intuitive incorporation of PFS and OS data from the clinical trial when estimating state membership. In the IMROZ trial, the primary and key secondary endpoints were the time-to-event outcomes PFS and OS, which correspond directly with the required survival functions used in a three-state PSM. Additionally, as MM is a chronic and incurable disease, patients do not need to move backwards between health states, further aligning with the PSM structure. This modelling approach is further supported by previous technology appraisals, including TA917 (72), TA763 (112), TA311 (113), and TA680 (114).

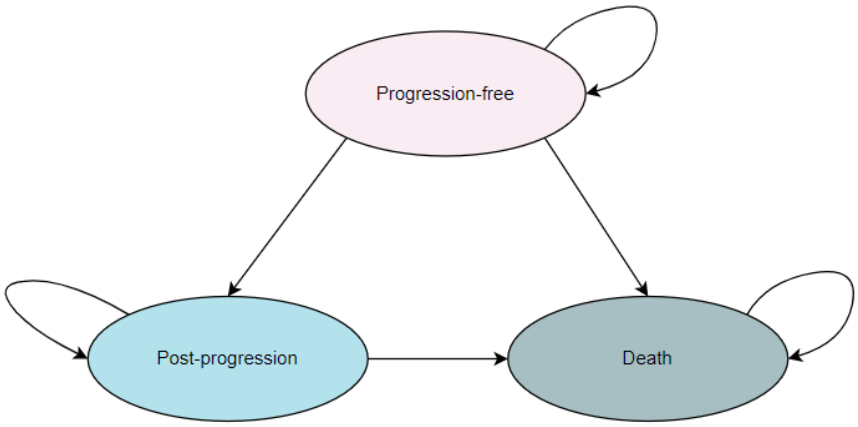
A substantive issue with Markov models is the lack of data on the distribution of post-progression survival (PPS) for all comparators as they were not included in the trial. Assumptions would need to be made about the PPS for those comparators for which data are not available. While a hybrid structure of a partitioned survival model (PSM) followed by a Markov model was used in TA587, the Committee criticised this approach and suggested that a partitioned survival analysis would have allowed for more flexible modelling of OS and PFS independently (73). Furthermore, MRD negativity was used as a surrogate endpoint in TA587, which also faced criticism (73).

Consequently, the PSM has been considered the most appropriate structure for this analysis. Additionally, PSMs have been accepted for decision-making in other evaluations of isatuximab in MM, such as in TA658 (115). Clinical expert interviews conducted by Sanofi also support this model selection.

Given that PFS and OS are modelled independently, the model has incorporated appropriate functionality to ensure that the estimates remain plausible across the modelled time horizon. In particular, PFS and OS are modelled to not intersect, with

general population mortality applied in the background. The three-state partitioned survival model structure is presented in Figure 32.

Figure 32: Model diagram



The model uses three mutually exclusive health states to assess patient outcomes:

- Progression-free state (PF)
- Post-progression state (PP)
- Death

The proportion of patients occupying each health state is calculated using PFS and OS curves. These curves are informed by IMROZ and statistical assessments as described in Section B.2.4.

All patients enter the model in the PF health state, where they are assumed to receive IsaVRd or a selected comparator. Patients remain in the PF health state until they experience disease progression or die. Within the PF health state, patients may or may not be receiving treatment; on-treatment/off-treatment statuses are modelled as distinct sub-health states of the PF health state, as all treatments are given maximally until progression. PFS data was sourced from IMROZ for IsaVRd and was determined by the Independent Central Review (ICR), while PFS for comparators not included in the IMROZ trial was derived from an indirect treatment comparison (ITC). After progression, patients move to the post-progression (PP) health state where they remain until death.

Costs and utilities are applied per health state:

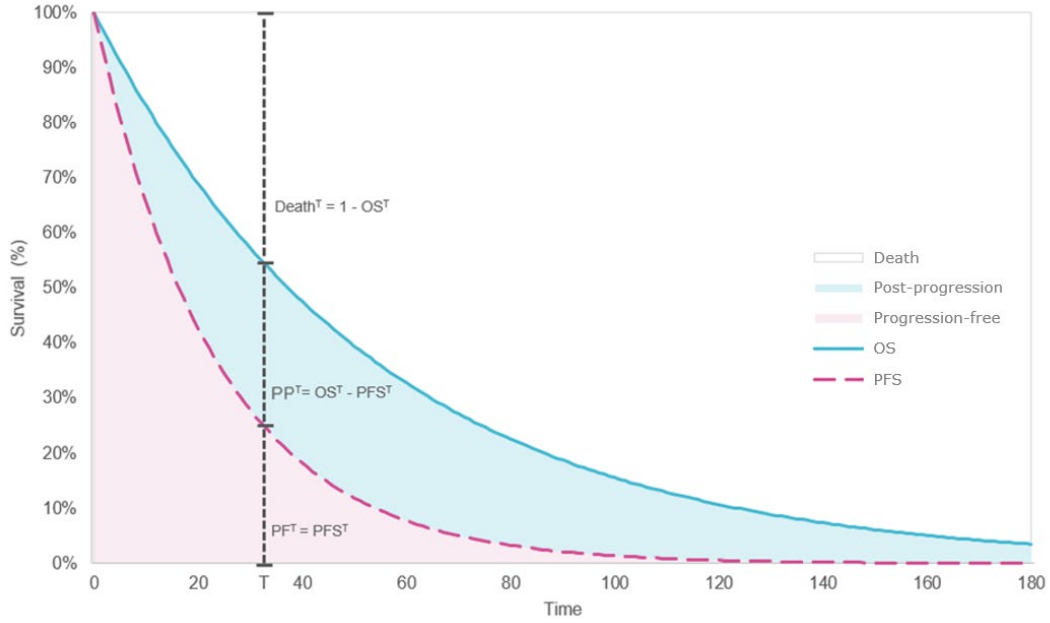
- Within the PF health state, patients incur the cost of the intervention or comparator according to their time on treatment (drug acquisition costs, drug administration costs); monitoring costs and drug-related AE costs are also applied within this health state, along with a PF utility and AE utility decrements
- Patients in the PP health state incur PP monitoring costs (116) and subsequent therapy costs and have a PP utility applied. Patients who transition to death incur end-of-life costs

This partitioned survival analysis uses independently fitted PFS and OS curves to calculate a health state's occupancy at a given time using the area under the curve approach. The proportion of patients in the PF state is calculated directly using the

extrapolated PF curve at time T (PF^T). The proportion of patients in the death health state is calculated as 1 – OS^T, where OS^T is the survivor function (the probability that a patient is alive) at time T. The proportion of patients in the PP state is equal to OS^T minus PF^T. Health state occupancy is shown graphically in Figure 33.

The OS rate is capped by the age and gender-matched general population mortality rate and all patients are assumed to be dead at 100 years old. The PFS rate is capped by the OS rate for the same time period to ensure that OS is always greater than PFS.

Figure 33: Health state occupancy at time T



Abbreviations: OS, overall survival; PP, post-progression; PF, progression-free; PFS, progression-free survival.

B.3.2.2.1 Time horizon and cycle length

A lifetime time horizon of 29 years is used in the base case. This assumes that all patients, starting at an average age of 71.63 years, will die by the age of 100 (refer to Section B.3.2.1). A cycle length of 14 days (2 weeks) is applied in the model. This cycle length is considered sufficiently short enough to accurately capture key clinical outcomes and dosing regimens of isatuximab with its comparators. A half-cycle correction is applied to costs or health outcomes in the base case.

B.3.2.2.2 Discounting

Both costs and health outcomes (LYs and QALYs) are discounted at 3.5% per annum in the model, in line the NICE reference case (117).

B.3.2.2.3 Perspective

In line with NICE guidance, the base case analysis takes the perspective from the NHS and Personal Social Services.

B.3.2.2.4 Features of the economic analysis

The additional features of the economic analysis are outlined and justified in Table 45.

Table 45: Features of the economic analysis

	Previous evaluation			Current evaluation	
Factor	**TA917**	**TA587**	**TA228**	**Chosen values**	**Justification**
Time horizon	26 years	Lifetime (25 years) Scenario analyses incorporate lifetimes of 15 and 35 years as scenario analyses	Lifetime (30 years)	Lifetime (29 years)	See Section B.3.2.2.1
Treatment waning effect?	The preferred committee assumption was that the modelled overall-survival hazard ratio would be fixed at the end of the observed period from the most recent MAIA data cut	No treatment waning effect	No treatment waning effect	The overall survival hazard ratio is fixed at the end of the IMROZ follow-up due to an improving treatment effect versus all comparators	There is no evidence to suggest whether, or when, the treatment effect of isatuximab on survival would wane over time. Following prior technology appraisal (TA917), the model adopts the assumption of a sustained treatment effect by fixing the HR to model a continued improvement in OS compared with all relevant comparators (72). This approach is supported by the improving treatment effect over time between IsaVRd and comparators and reflects an ongoing treatment benefit rather than a waning effect, which is not applied in the base-case scenario. The rationale against applying a waning effect stems from the mechanism of action of isatuximab, which modulates the immune system to maintain its therapeutic efficacy (Section B.1.2). In the IMROZ study, the percentage of patients achieving minimal residual disease (MRD)–negative status was significantly higher in the IsaVRd group compared with the VRd group. Specifically, 55.5% of patients in the IsaVRd group reached MRD-negative status, whereas only 40.9% of patients in the

	Previous evaluation			Current evaluation	
Factor	**TA917**	**TA587**	**TA228**	**Chosen values**	**Justification**
					VRd group achieved this status (odds ratio [OR]: 1.80 [95% CI, 1.23–2.65; P = 0.003]). This indicates a notable improvement in the depth of response when isatuximab is added to the VRd regimen, suggesting that the combination therapy is more effective in eradicating residual disease in patients with newly diagnosed multiple myeloma who are ineligible for transplantation. In comparison, the MAIA study, which evaluated DRd, reported that 31% of patients achieved MRD-negative status at a sensitivity threshold of 10^{-5} (77). This comparison highlights the superior MRD-negative rates achieved with the IsaVRd regimen in the IMROZ study compared with the DRd regimen in the MAIA study. The prognostic significance of MRD and its association with improved PFS/OS is well established in newly diagnosed MM (including transplant-ineligible patients) with results from IMROZ
Source of utilities	Utilities for pre- and post-progression were derived from MAIA. EQ-5D-5L scores from MAIA were cross walked to 3L using the mapping function developed by Hernández Alava et al. 2017 (118)	Rd and MPT use EQ-5D data from the MM-020 trial. For VMP, QLQ-C30 data from VISTA (Delforge et al. 2012 (119)) were mapped to EQ-5D using Proskorovsky et al. 2014 (120)	Gulbrandsen and colleagues from the mapping by McKenzie and van der Pol. (0.58 for treatment period, and 0.68 for post-treatment) (121, 122)	EQ-5D-5L from IMROZ trial mapped to EQ-5D-3L for PFS. PPS utility value is sourced from the literature	The approach aligns with the NICE reference case, utilising EQ-5D-5L from the IMROZ trial mapped to EQ-5D-3L for progression-free survival (PFS). For post-progression survival (PPS), insufficient data points were available to provide a reliable and accurate assessment of quality of life directly from trial data. As a result, using PPS utility values from the literature was necessary, acknowledging that this may not fully capture the true quality of life during this phase but ensures an evidence-based estimate is applied.

	Previous evaluation			Current evaluation	
Factor	**TA917**	**TA587**	**TA228**	**Chosen values**	**Justification**
Source of costs	NHS reference costs, the BNF and pharmaceutical electronic market information tool (eMIT).	BNF; eMIT; NHS Reference Costs	BNF; eMIT; NHS Reference Costs	BNF 2023; eMIT 2023; NHS Reference Costs 2022-23	In accordance with the NICE manual, we selected cost sources that adhere to its recommendations for using the most up-to-date and relevant national sources (117). The BNF 2023 is referenced for medication costs, as it provides widely accepted and current drug pricing in the UK healthcare setting. The eMIT 2023 is used for procurement costs, reflecting the most recent national average prices paid by NHS trusts for medicines. NHS Reference Costs 2022-23 are employed for health services resource use, as they provide detailed and standardised costing information for NHS procedures and treatments, in line with the NICE guidance to ensure consistency and transparency in economic evaluations.

Abbreviation: BNF, British National Formulary; eMIT, electronic market information tool; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer core quality of life 30-item questionnaire; EQ-5D-5L, EuroQol-5 Dimensions-5 Level; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; MPT, melphalan, prednisone, and thalidomide; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; VMP, bortezomib, melphalan and prednisone.

B.3.2.3 *Intervention technology and comparators*

The intervention of interest in this model is IsaVRd. Treatment is provided in two phases in line with the IMROZ clinical trial protocol (123):

- Induction treatment, IsaVRd (24 weeks)
- Continuous treatment, IsaRd (until disease progression, unacceptable AE, or participant's decision to discontinue (123))

The dosing regimen for each treatment phase is informed by the IMROZ trial (Table 8). Patients with moderate renal impairment, defined as creatinine clearance between 30 and 60 mL/min, receive a reduced dose of lenalidomide.

As per the final scope for this appraisal, the relevant comparators are DRd, Rd, VCd, and VMP (124). DRd, VMP, and Rd are modelled as per licences (Table 46). Dosing schedules were taken from the summary of product characteristics and/or clinical trial protocols. No appropriate clinical trials were available for VCd; therefore, VCd dosing was taken from NHS dosing protocols, which was identified as the most robust published data source in the absence of relevant clinical trials (125). Daratumumab is assumed to be administered by subcutaneous injection.

Table 46: Drug dosing schedules

Comparators	Treatment phase*	Duration/ cycles	Drug	Administration	Dose	Schedule	Reference
IsaVRd	Induction (IsaVRd)	Induction therapy (4 x 6 weeks)	Isatuximab	IV	10 mg/kg	Cycle 1: Day 1, 8, 15, 22, 29. Cycle 2-4: Day 1, 15, 29	SmPC (2)
			Bortezomib	SC	1.3 mg/m2	Day 1, 4, 8, 11, 22, 25, 29, 32	
			Lenalidomide	Oral	25 mg (10mg[b])	Day 1–14 and 22-35	
			Dexamethasone	IV	20 mg	Cycle 1: Day 1, 8, 15, 22, 29. Cycle 2-4: Day 1, 15, 29	
			Dexamethasone	Oral	20 mg	Cycle 1: Day 2, 4, 5, 9, 11, 12, 23, 25, 26, 30, 32, 33	
	Continuous (IsaRd)	Continuous therapy (4 weeks until progression)	Isatuximab	IV	10 mg/kg	Cycle 1–13 (52 weeks) (5–17): Day 1, 15. Cycle 14+ (18+a): Day 1	
			Lenalidomide	Oral	25 mg (10 mg[b])	Day 1–21	
			Dexamethasone	IV	20 mg	Cycle 1–13 (52 weeks) (5–17): Day 1, 15. Cycle 14+ (18+a): Day 1	
			Dexamethasone	Oral	20 mg	Cycle 1–13 (52 weeks) (5–17):	

Comparators	Treatment phase*	Duration/ cycles	Drug	Administration	Dose	Schedule	Reference
						Day 8, 22. Cycle 14+ (18+a): Day 8, 15, 22	
DRd	Induction (DRd)	6 x 4 weeks	Daratumumab	IV[a]	16 mg/kg	Cycle 1 and 2: 1, 8, 15, 22. Cycle 3–6: 1, 15	Darzalex SmPC (126) (MAIA*); NICE TA917 (72)
			Daratumumab	SC[b]	1,800 mg	Cycle 1 and 2: 1, 8, 15, 22. Cycle 3–6: 1, 15	
			Lenalidomide	Oral	25 mg (10 mg[b])	Days 1–21	
			Dexamethasone	IV	40 mg	Cycle 1: Day 1	
			Dexamethasone	Oral	40 mg	Cycle 1: Days 8, 15, 22. Cycle 2–6: Days 1, 8, 15, 22	
	Continuous	4 weeks until progression	Daratumumab	IV[a]	16 mg/kg	Day 1	
			Daratumumab	SC[a]	1,800 mg	Day 1	
			Lenalidomide	Oral	25 mg (10 mg[b])	Days 1–21	
			Dexamethasone	Oral	40 mg	Days 1, 8, 15, 22	
VCd	Single regimen	8 x 3 weeks	Bortezomib	SC	1.3 mg/m^2	Days 1, 8, 15	
			Cyclophosphamide	Oral	500 mg	Days 1, 8, 15	

Comparators	Treatment phase*	Duration/ cycles	Drug	Administration	Dose	Schedule	Reference
			Dexamethasone	Oral	20 mg	Days 1, 2, 8, 9, 15, 16	NHS England (125)
VMP	Induction (VMP)	4 x 6 weeks	Bortezomib	IV	1.3 mg/m^2	Days 1, 4, 8, 11, 22, 25, 29, 32	Velcade SmPC (127) (VISTA)
			Melphalan	Oral	9 mg/m^2	Days 1–4	
			Prednisone	Oral	60 mg/m^2	Days 1–4	
	Continuous (VMP)	5 x 6 weeks	Bortezomib	IV	1.3 mg/m^2	Days 1, 8, 22, 29	
			Melphalan		9 mg/m^2	Days 1–4	
			Bortezomib	Oral	1.3 mg/m^2	Days 1, 4, 8, 11, 22, 25, 29, 32	
Rd	Single regimen	4 weeks until progression	Lenalidomide	SC	25 mg (10 mg[b])	Days 1–21	Revlimid SmPC (128) (FIRST)
			Dexamethasone	Oral	40 mg	Days 1, 8, 15, 22	

Abbreviations: CrCl, creatinine clearance; DRd, daratumumab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; IsaRd, isatuximab, lenalidomide, and dexamethasone; IV, intravenous; NICE, National Institute of Health and Care Excellence; Rd, lenalidomide and dexamethasone; SC, subcutaneous; SmPC, Summary of Product Characteristics; TA, technology appraisal; VCd, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

Notes: [a] Daratumumab can be administered either intravenously or subcutaneously in the model. Both dosing regimens are included for clarity [b] Dose for patients with CrCl ≥30 to <60 mL/min.*In the MAIA trial, daratumumab was administered intravenously to the DRd group. More recently, daratumumab has become available as a SC formulation and in line with NICE TA917 is recommended in SC form.

B.3.3 *Clinical parameters and variables*

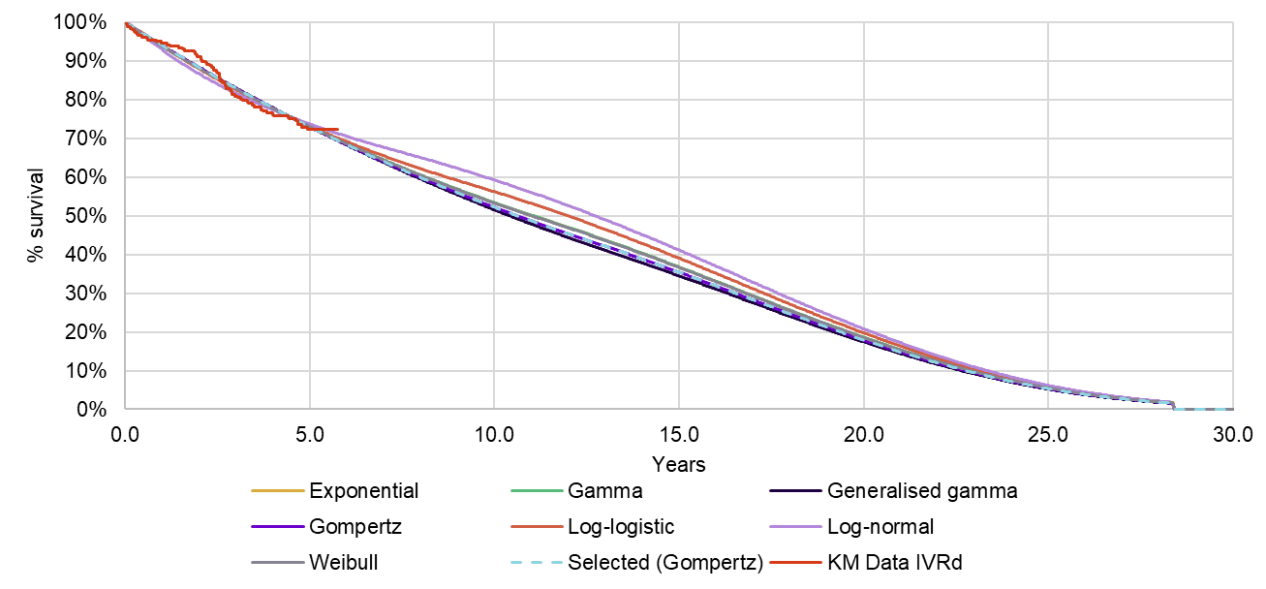
B.3.3.1 *Overall survival extrapolation*

When selecting a parametric survival model to enable long-term extrapolation beyond the end of study follow-up, one of the key choices was whether to fit a proportional hazards model that includes a term for the relative effect of treatment between study arms (the hazard ratio), or to fit models separately to each arm of the trial. NICE TSD 14 recommends an assessment of whether the proportional hazards assumption holds, but notes that when patient-level data are available, it is unnecessary to rely on this assumption (129). Therefore, parametric models were fit separately to IsaVRd and VRd. Additionally, VRd is not a comparator of interest and its extrapolation will only be used in the scenario with the standard NMA. As previously described, the base-case uses a MAIC and does not rely on the VRd survival.

B.3.3.1.1 IsaVRd

Parametric models were fit to the IsaVRd arm of the IMROZ study based on the guidance from NICE TSD 14 (130). The Gompertz was chosen as the base case distribution, and generalized gamma distributions as a scenario, though both provide a suitable fit to the OS data for the IsaVRd arm of IMROZ based on visual inspection on IMROZ follow-up, model fit statistics, smoothed and parametric hazard functions and external validation. OS IsaVRd extrapolations are presented in Figure 34.

Figure 34: Overall survival for IsaVRd (lifetime time horizon – adjusted for general population mortality)

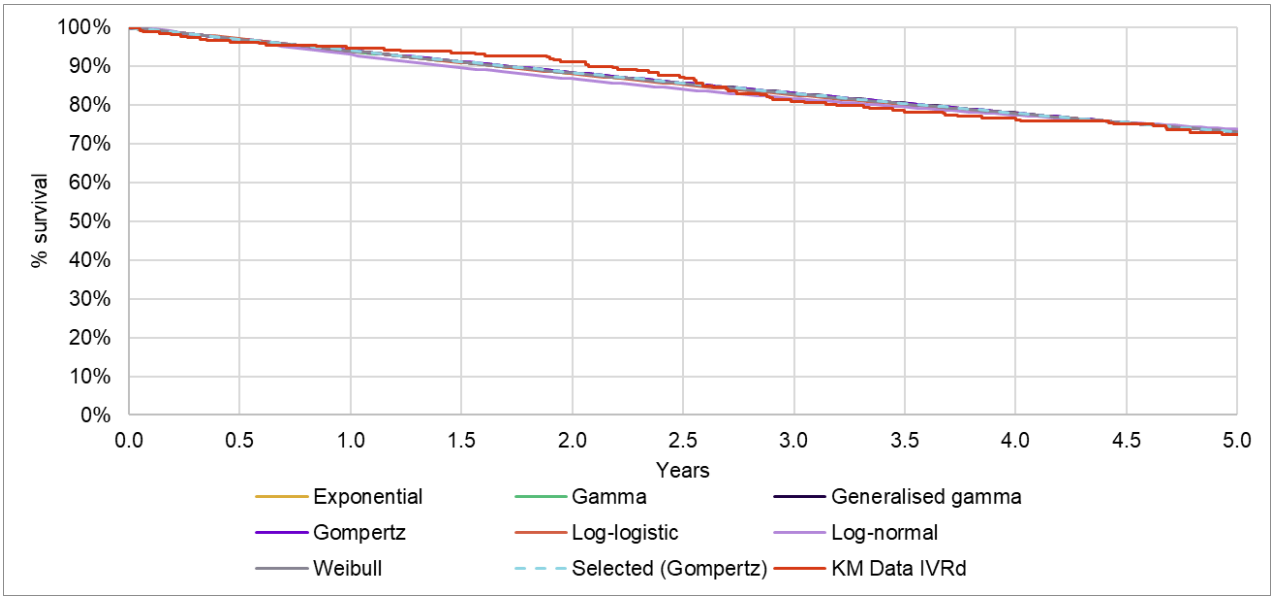


Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; KM, Kaplan–Meier.

Visual Inspection

Figure 35 shows the fit of the seven standard parametric models fit on the IMROZ follow-up. Visually, all provide a good fit over the IMROZ clinical study period.

Figure 35: Overall survival for IsaVRd (5-year time horizon)



Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; KM, Kaplan–Meier.

Model fit statistics

AIC and BIC values are provided for the standard parametric curves in Table 47. For AIC, all models, except Log-normal, are within five points of each other, indicating that there is little meaningful difference between the remaining models regarding the goodness of fit to the observed data. For BIC, Exponential fits better than the other models. Gompertz, Weibull, Gamma and log-logistic are within six points of the best fitting model. Log-normal and generalized gamma do not fit well with more than ten points from the best fitting model. Overall, according to both AIC and BIC, the Exponential distribution fits best, followed by Gompertz, Weibull, Gamma and Log-logistic.

Table 47: Fit statistics of overall survival extrapolation – IsaVRd

Distribution	AIC	AIC rank	AIC delta	BIC	BIC rank	BIC delta
Exponential	865	1	0.00	869	1	0.00
Gamma	867	4	2.00	874	4	5.58
Generalised gamma	869	6	3.86	880	7	11.02
Gompertz	867	2	1.98	874	2	5.56
Log-logistic	867	5	2.40	875	5	5.98
Log-normal	872	7	7.08	879	6	10.66
Weibull	867	3	2.00	874	3	5.58

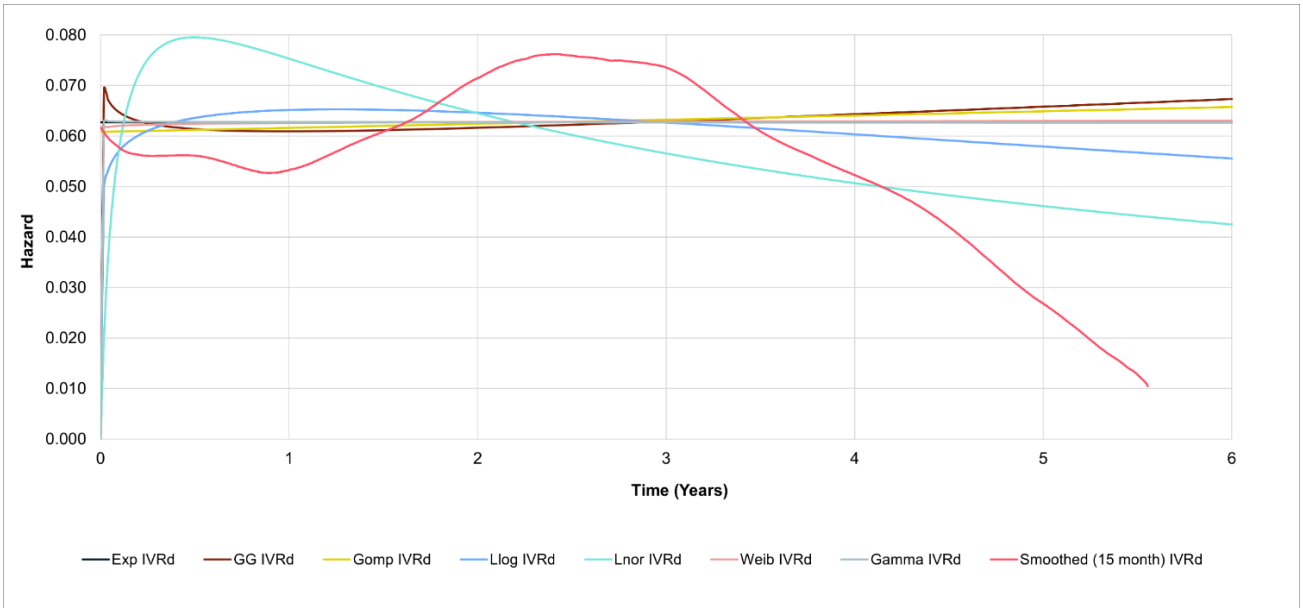
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone.
Notes: AIC and BIC values are rounded to the nearest integer. Cells shaded in yellow are within five points of the best fitting model. Cells shaded in blue are within five points of the second-best-fitting model.

Smoothed and parametric hazards

As shown in Figure 36, the smoothed hazard plot for IsaVRd indicates that the hazard is increasing up to 3 years and then decreases. The hazard for IsaVRd during the trial period could be considered as initially increasing followed by decreasing; therefore, the log-logistic and log-normal would theoretically provide the correct shaped hazard function. However, these distributions did not provide good fit in terms of AIC and/or BIC. Additionally, a decreasing hazard over time seems implausibly optimistic. The exponential distribution has the best goodness of fit, but it assumes a constant hazard over time that does not align with the shape of the smoothed hazard. Additionally, using the exponential distribution would assume a constant HR with other comparators after adjustment with MAICs as the same distribution is used across comparators. As described in Appendix D.3, PH tests after adjustments suggest a violation of the assumption of IsaVRd versus comparators.

The Generalised gamma, Gompertz, Weibull, and Gamma predict similar hazards to each other, with a slightly increasing hazard after 3 years. The Generalised gamma does not have a good fit in terms of BIC but provides realistic hazards. According to statistical fit and hazard shape, Gompertz and Generalised gamma and seem to provide the most realistic options and could be considered conservative extrapolation choices.

Figure 36: Overall survival – IMROZ ITT population – smoothed hazards with parametric survival models fit separately to IsaVRd



Abbreviations: Exp, exponential; Gamma, gamma; GG, generalised gamma; Gomp, Gompertz; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; ITT, intention-to-treat; Llog, log-logistic; Lnor, log normal; VRd, bortezomib, lenalidomide, and dexamethasone; Weib, Weibull.

External validation

Figure 34 shows the extrapolations beyond the end of the trial period up to a lifetime time horizon. Consistent with all other OS extrapolations, they are adjusted by age- and gender-matched background mortality calculated using the 2017–2019 Office for National Statistics life tables for England, in line with TSD 23 (131). Visually, on the time horizon, little survival difference is observed between the different models. Table 48 shows the predicted probability of patients alive at 5, 10, 15 and 20 years. The Generalised Gamma and Gompertz distributions have the lowest survival rates, approximately 52% at 10 years, 35% at 15 years, and 18% at 20 years. These rates were very close to the upper limits of the survival estimates collected during clinician expert

interviews, which were 45% (95% CI; 35, 55) at 10 years, 24% (95% CI; 15, 33) at 15 years, and 11% at 20 years (95% CI; 5, 17). More information on clinical expert interviews is available in B.3.3.6.

Therefore, Generalised gamma and Gompertz distributions provide the most plausible estimates for IsaVRd OS. Gompertz was chosen in the base case due to a better fit statistic.

Table 48: Proportion of patients alive at key time points (adjusted for general population mortality) – IsaVRd

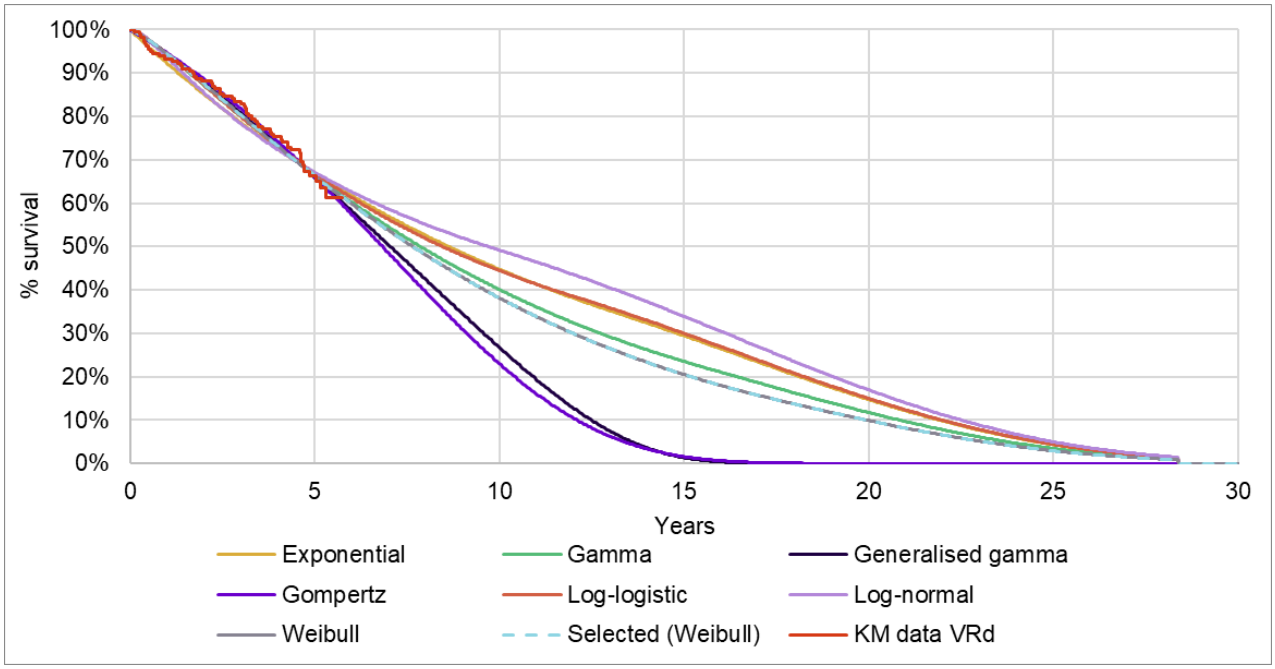
Distribution	Modelled landmarks			
	5 years	10 years	15 years	20 years
	60 months	120 months	180 months	240 months
Exponential	73.16%	53.53%	36.72%	18.69%
Gamma	73.16%	53.55%	36.84%	18.70%
Generalized gamma	73.11%	51.70%	34.50%	17.56%
Gompertz	73.12%	52.36%	35.40%	18.02%
Log-logistic	73.30%	56.34%	38.97%	19.84%
Log-normal	73.82%	59.37%	41.01%	20.88%
Weibull	73.15%	53.42%	36.62%	18.64%
IsaVRd – Clinical experts (95% CI)	-	45% (35, 55)	24% (15, 33)	11% (5, 17)

Abbreviations: CI, confidence interval; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone.

B.3.3.1.2 VRd

Parametric models were fit to the IsaVRd arm of the IMROZ study based on the guidance from NICE TSD 14 (130). The Weibull was chosen as the base case extrapolation distribution based on visual inspection on IMROZ follow-up, model fit statistics, smoothed and parametric hazard functions and external validation. OS VRd extrapolations are presented in Figure 37.

Figure 37: Overall survival for VRd (lifetime time horizon – adjusted for general population mortality)

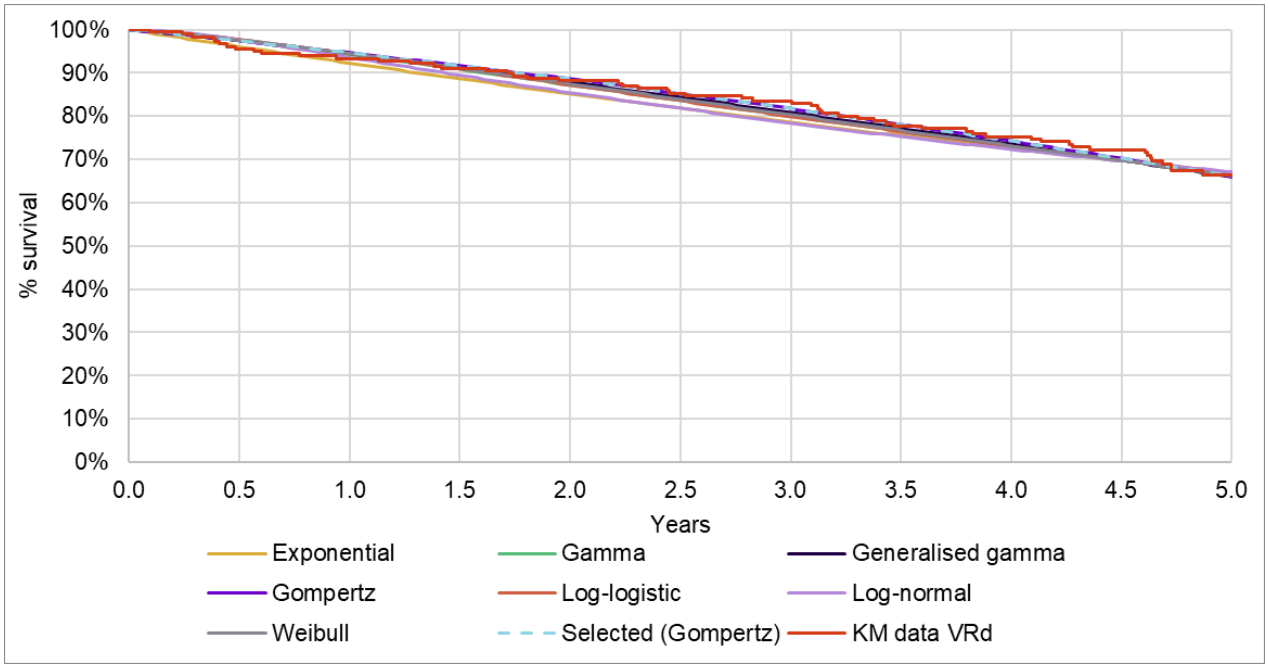


Abbreviations: KM, Kaplan–Meier; VRd, bortezomib, lenalidomide and dexamethasone.

Visual Inspection

Figure 38 shows the fit of the seven standard parametric models for VRd in the IMROZ clinical study period (exponential, Weibull, Gompertz, log-logistic, log-normal, gamma and generalised gamma). Visually, all seven provide a good fit over the IMROZ clinical study period.

Figure 38: Overall survival for VRd (5-year time horizon – adjusted for general population mortality)



Abbreviations: KM, Kaplan–Meier; VRd, bortezomib, lenalidomide and dexamethasone.

Model fit statistics

AIC and BIC values are provided for the standard parametric curves in Table 49. For AIC, all models, except log-normal, are within five points of each other, indicating that there is little meaningful difference between the remaining models in terms of goodness of fit to the observed data. For BIC, Exponential, Gompertz, Weibull, Gamma and Log-logistic are within five points of the best fitting model. Log-normal and generalised gamma fit less well with more than 6 points from the best fitting model. Overall, according to both AIC and BIC, Gompertz, Weibull, Exponential, Gamma and Log-logistic fit well.

Table 49: Fit statistics of overall survival extrapolation – VRd

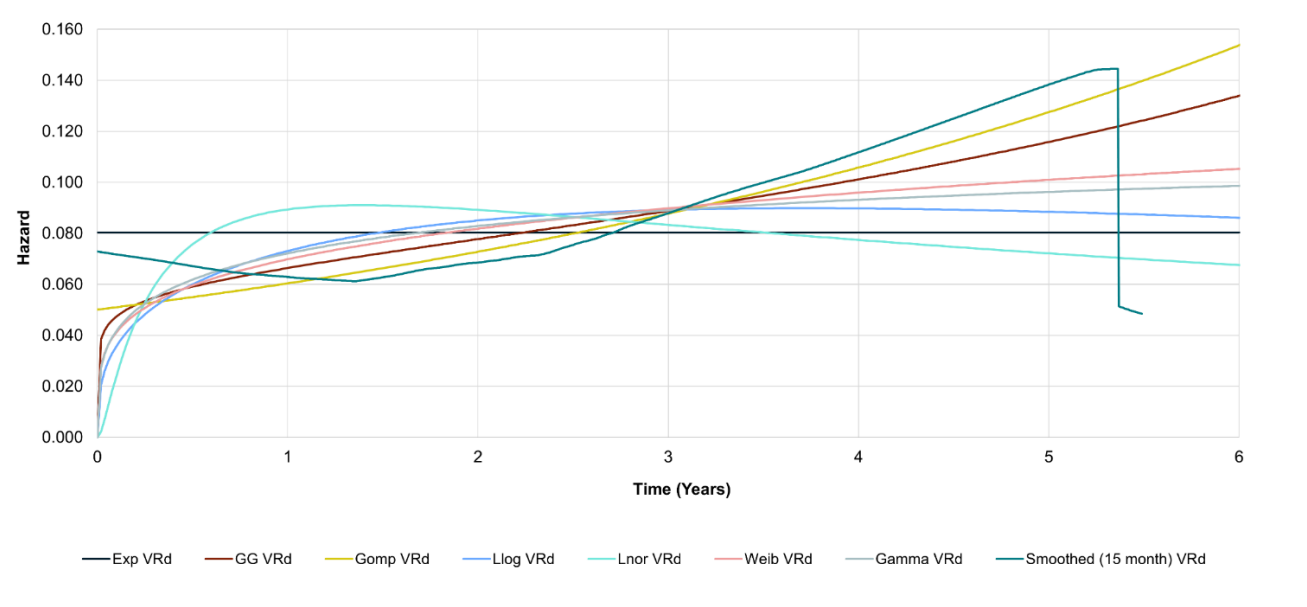
Distribution	AIC	AIC rank	AIC delta	BIC	BIC rank	BIC delta
Exponential	710.8	4	2.4	714.0	1	0.0
Gamma	710.5	3	2.2	716.9	4	2.9
Generalized gamma	710.8	5	2.5	720.4	6	6.5
Gompertz	708.4	1	0.00	714.8	2	0.8
Log-logistic	711.8	6	3.4	718.2	5	4.2
Log-normal	715.2	7	6.8	721.6	7	7.6
Weibull	710.1	2	1.8	716.5	3	2.6

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival; VRd, bortezomib, lenalidomide and dexamethasone.
Notes: AIC and BIC values are rounded to the nearest integer. Cells shaded in yellow are within five points of the best fitting model.

Smoothed and parametric hazards

The smoothed hazard for the VRd arm of the IMROZ study showed that the hazard was constant up to 2 years and then increases (Figure 39). This plot suggests that the VRd hazards could be interpreted as monotonically increasing, though this should be interpreted cautiously and not over interpreted as the exact shape can be sensitive to the degree of smoothing, especially for the tail. The Log-normal and Log-logistic models assume hazards that initially increase and decrease, which would not fit the smoothed hazard. As the hazard increases, this rules out the exponential, which assumes a constant hazard. The remaining alternatives can all model monotonically increasing hazards. Overlaying the hazards from the parametric survival models with the smoothed hazards observed in IMROZ indicates that the Generalised gamma and Gompertz distributions fit the VRd data well towards the end of the study follow-up period. Additionally, Weibull and Gamma also model an increasing hazard over time (Figure 39).

Figure 39: Overall survival – IMROZ ITT population – smoothed hazards with parametric survival models fit separately to VRd



Abbreviations: Exp, exponential; Gamma, gamma; GG, generalised gamma; Gomp, Gompertz; IVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; ITT, intention-to-treat; Llog, log-logistic; Lnor, log-normal; VRd, bortezomib, lenalidomide, and dexamethasone; Weib, Weibull.

External validation

Figure 37 shows the extrapolations beyond the end of the trial period up to a lifetime time horizon. VRd survival outcomes includes the survival of patients over the long term, which was reflected through age- and gender-matched background mortality calculated using the 2017–2019 Office for National Statistics life tables for England, in line with TSD 23 (131). Visually, there is some variation between the alternative models despite the similar fit to the observed data. Table 50 shows the predicted probability of patients alive at 5, 10, 15 and 20 years. The log–normal, log-logistic, and exponential distributions show the highest survival rates over time, with log-normal showing 17.3%, log-logistic 15.3%, and exponential 15.0% at 20 years.

The Gompertz distribution shows the lowest survival rates, with approximately 23% at 10 years, 2% at 15 years, and 0% at 20 years. These rates are lower than the survival estimates gathered from clinician expert interviews, which were 33% (95% CI; 26, 40) at 10 years, 16% (95% CI; 8, 23) at 15 years, and 4% (95% CI; 2, 12) at 20 years. The Weibull distribution, which is the second-best fit, aligns more closely with clinicians' opinions, showing survival rates of 38% at 10 years, 21% at 15 years, and 10% at 20 years. Additionally, this is the only distribution with all survival rates falling within the confidence intervals provided by clinicians. Therefore, Weibull provide the most plausible estimates for VRd OS and was chosen for the scenario with the NMA. More information on clinical expert interviews is available in B.3.3.6.

Table 50: Proportion of patients alive at key time points (adjusted for general population mortality) – VRd

Distribution	Modelled landmarks			
	5 years	10 years	15 years	20 years
	60 months	120 months	180 months	240 months
Exponential	67.01%	44.91%	29.51%	15.02%
Gamma	66.55%	40.23%	23.54%	11.93%
Generalised gamma	66.11%	27.00%	1.35%	0.00%
Gompertz	66.23%	23.27%	1.59%	0.00%
Log-logistic	66.94%	44.55%	30.10%	15.32%
Log-normal	67.23%	49.27%	34.06%	17.34%
Weibull	66.43%	38.33%	20.52%	10.02%
VRd – Clinical experts (95% CI)	-	33% (26-40)	16% (8-23)	4% (2-12)

Abbreviations: CI, confidence interval; VRd, bortezomib, lenalidomide and dexamethasone.

B.3.3.1.3 Comparators not included in IMROZ

Justification for time-varying HR

In the absence of head-to-head clinical trials between IsaVRd and comparators of interest, MAICs and IPW were conducted. PH assumption was tested between IsaVRd and comparators after matching. Diagnostic tests indicate that PH does not hold between IsaVRd and all other comparators. Full details are presented in Appendix I.5. Therefore, an approach that relaxes the PH assumption is preferred and used in the base-case. Constant HR MAICs and IPW will be tested in a scenario analysis.

For implementation in the cost-effectiveness model, the time-varying HRs from ITCs were anchored to the IsaVRd curve selected from fitting parametric survival models to the IMROZ ITT data. According to NICE DSU TSD 14, it is recommended to use the same distribution across comparators. Additionally, although the survival of IsaVRd may change when matching to the comparator population in the MAICs, there is no obvious reason to think the survival for IsaVRd would follow a different distribution with different comparators. Therefore, the same distribution was used to estimate time-varying HR after matching and for the IsaVRd distribution in the model. For OS, Gompertz distribution is used. Time-varying HRs for Gompertz are presented in Table 51. HRs for overall survival are presented at various time points, comparing IsaVRd with DRd, Rd, VMP, and VCd. Values are less than 1 and suggest a survival benefit for IsaVRd compared to the comparators. The different HRs suggest an improving treatment effect over time of IsaVRd versus all comparators. The time-varying HRs between IsaVRd and DRd, Rd, VMP, and VCd for all distributions are described in Appendix I.5. Fit statistics for IsaVRd after matching are presented in Appendix I.5.

Table 51: Landmark HRs for overall survival – Gompertz distribution

Time (years)	HR (95% CI) for IsaVRd versus comparators			
	DRd	Rd	VMP	VCd
1	[redacted]	[redacted]	0.66 (0.43, 1.01)	0.51 (0.32, 0.82)
2	[redacted]	[redacted]	0.56 (0.40, 0.78)	0.47 (0.32, 0.68)
5	[redacted]	[redacted]	0.34 (0.17, 0.66)	0.36 (0.20, 0.62)
5.67*	[redacted]	[redacted]	0.30 (0.13, 0.67)	0.33 (0.17, 0.65)
10	[redacted]	[redacted]	0.15 (0.03, 0.79)	0.22 (0.06, 0.94)
28	[redacted]	[redacted]	0.01 (0.00, 1.94)	0.04 (0.00, 5.32)

Abbreviations: CI, confidence interval; DRd, daratumumab, lenalidomide, and dexamethasone; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone.
* End of IMROZ follow-up

Fixed treatment effect from the end of IMROZ trial follow-up for OS

The HRs of IsaVRd versus all comparators were fixed at the end of the IMROZ trial follow-up and for the remainder of the model time horizon due to an improving relative treatment effect for OS of IsaVRd compared with all comparators. According to the NICE TA917, the Committee agreed that the HR should be fixed from the end of the follow-up period to adopt a conservative approach considering the improving HR over time and the absence of longer-term data. A scenario will be tested in which the HR is not fixed.

Final overall survival for IsaVRd and all comparators is described in Figure 40. IsaVRd demonstrated a better survival benefit than all comparators and is followed by DRd and Rd. VCd and VMP come next but with similar OS outcomes.

Figure 40: Overall survival for IsaVRd, DRd, Rd, VMP, and VCd (lifetime time horizon – adjusted for general population mortality)

A: IsaVRd vs DRd; B: IsaVRd vs Rd; C: IsaVRd vs VMP; D: IsaVRd vs VCd.
Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; KM, Kaplan-Meier; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; Rd, lenalidomide and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

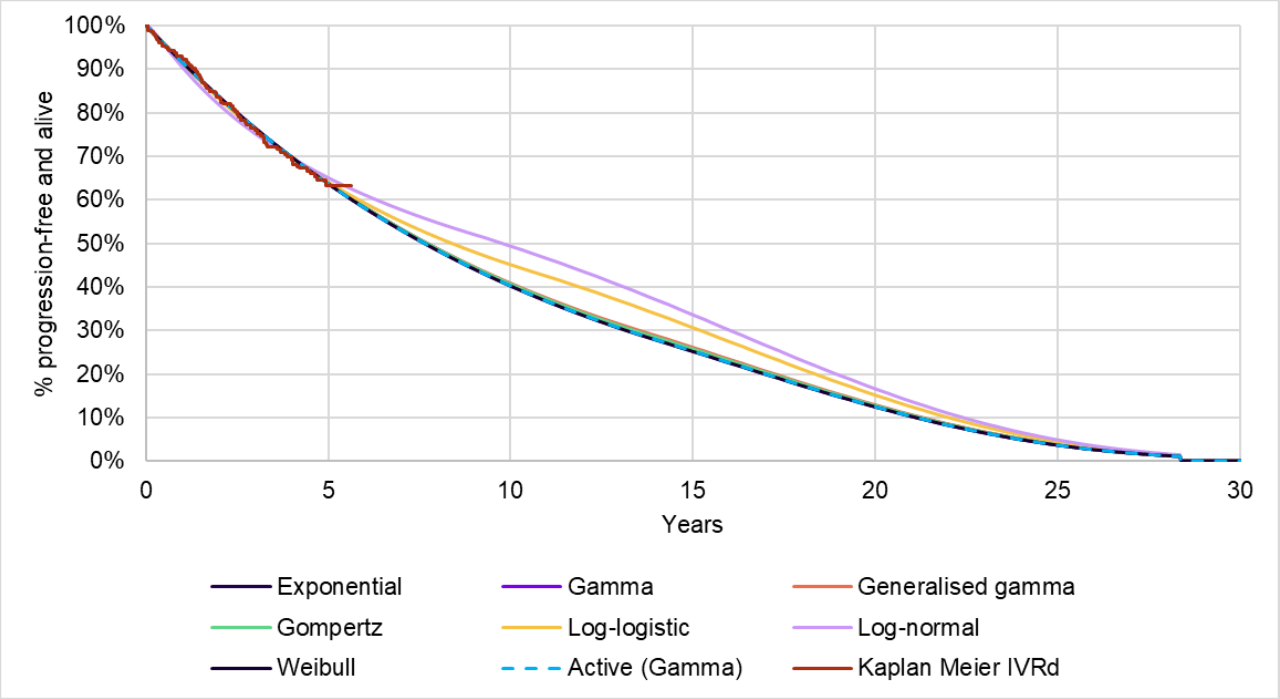
B.3.3.2 *Progression-free extrapolation*

In line with overall survival, parametric models were fit separately to each arm of the IMROZ trial. This approach follows the guidance from NICE TSD 14, which states that PH assumption is unnecessary when patient-level data are available. Additionally, VRd is not a comparator of interest, and its extrapolation will only be used in the scenario with the standard NMA. As previously described, the base-case uses a MAIC and does not rely on the VRd survival.

B.3.3.2.1 IsaVRd

Parametric models were fit to the IsaVRd arm of the IMROZ study based on the guidance from NICE TSD 14 (130). The Gamma was chosen as the base-case distribution and Gompertz and Weibull as scenario analyses. The choice is based on visual inspection on IMROZ follow-up, model fit statistics, smoothed and parametric hazard functions and external validation. PFS IsaVRd extrapolations are presented in Figure 41.

Figure 41: Progression-free survival for IsaVRd (lifetime time horizon – adjusted for general population mortality hazards)

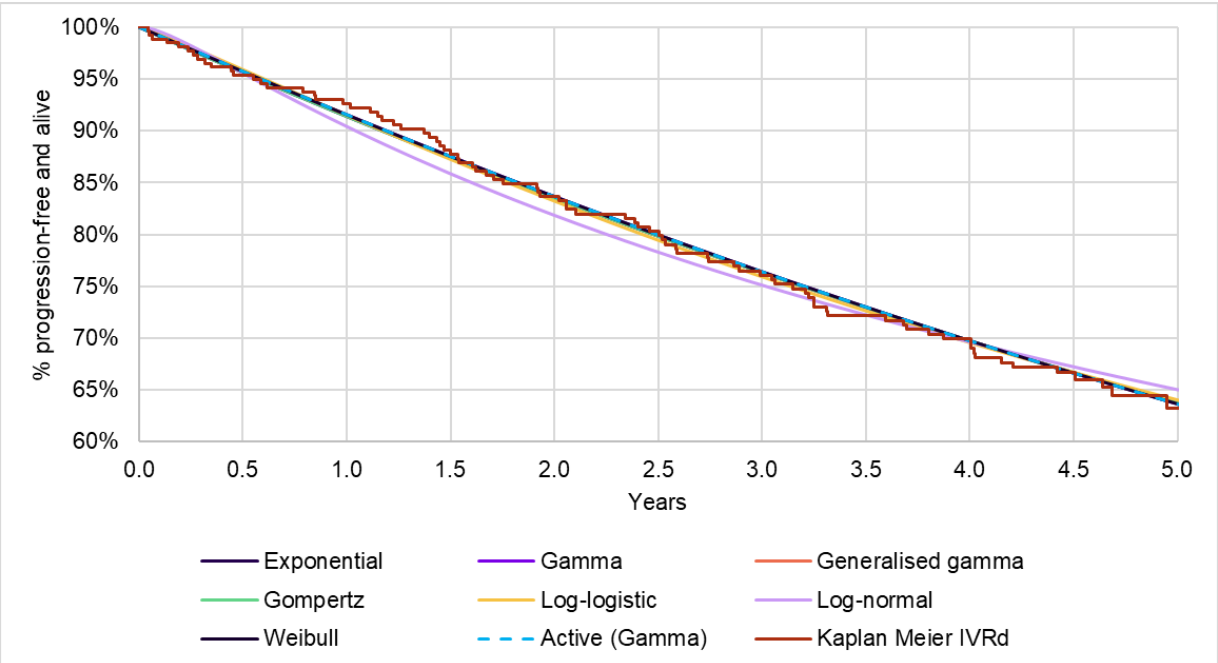


Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; KM, Kaplan-Meier.

Visual inspection

Figure 42 shows the fit of the different survival models to the IsaVRd IMROZ study data over the study follow-up period. Visually, all models showed a similar fit to the study data during the study period, except the log-normal that seems to underestimate survival until Year 4, followed by an overestimation at the end of the follow-up.

Figure 42: Progression-free survival for IsaVRd (5-year time horizon – adjusted for general population mortality hazards)



Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone.

Model fit statistics

AIC and BIC values are provided for the standard parametric curves in Table 52. The AIC statistic for all seven models was within five points of each other except for Log-normal which is within six points of the best fitting curve, indicating that there is little meaningful difference between the remaining models regarding the goodness of fit to the observed data. For BIC, Exponential fits better than the other models. Gamma, Weibull, Gompertz and Log-logistic are within six points of the best fitting model. Log-normal and Generalized gamma do not fit well with more than nine and eleven points from the best fitting model. Overall, according to both AIC and BIC, the Exponential distribution fits best, followed by Gamma, Weibull and Gompertz. However, the Log-normal does not fit well the observed data on IMROZ follow-up.

Table 52: Fit statistics of extrapolation – IsaVRd

Distribution	AIC	AIC rank	AIC delta	BIC	BIC rank	BIC delta
Exponential	991.8	1	0.0	995.4	1	0.0
Gamma	993.8	2	2.0	1000.9	2	5.5
Generalised gamma	995.8	6	4.0	1006.5	7	11.1
Gompertz	993.8	4	2.00	1001.0	4	5.6
Log-logistic	993.9	5	2.10	1001.1	5	5.7
Log-normal	997.4	7	5.60	1004.6	6	9.2
Weibull	993.8	3	2.0	1000.9	3	5.5

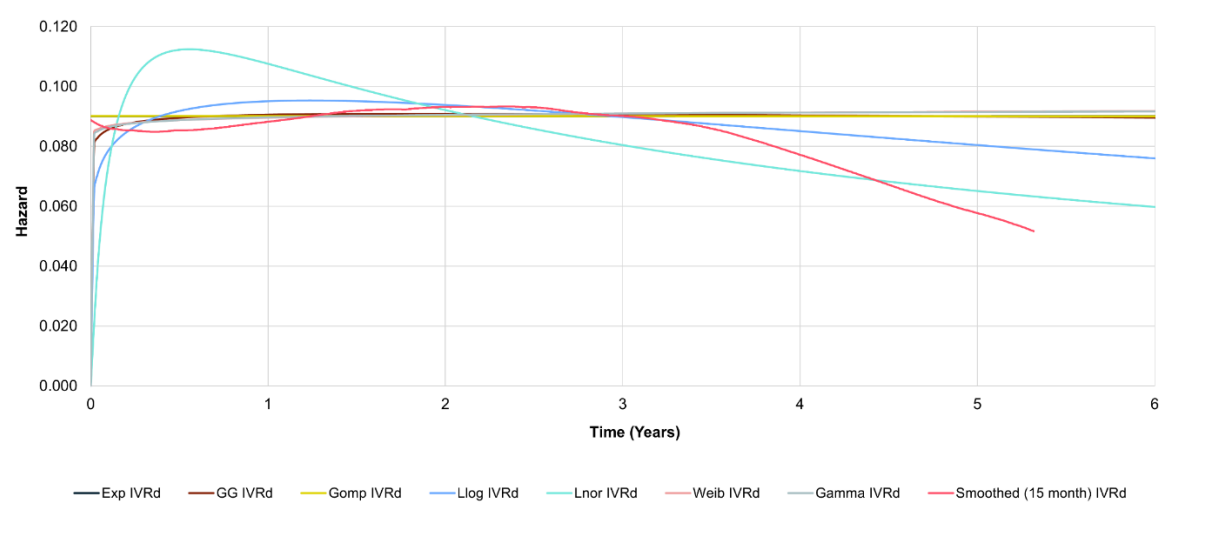
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.
Notes: AIC and BIC values are rounded to the nearest integer. Cells shaded in yellow are within five points of the best fitting model. Cells shaded in blue are within five points of the second-best fitting model.

Smoothed and parametric hazards

As seen in Figure 43, a smoothed hazards plot was explored. The exponential, gamma, generalized gamma, Gompertz and Weibull distributions have been a good fit for the IsaVRd data for approximately 3 years. After 3 years, there is a decrease in hazard for patients treated with IsaVRd. The log-logistic and log-normal distributions captured a decreasing hazard after 3 years, however, a decreasing hazard over time seems implausibly optimistic. The exponential distribution has the best goodness of fit but it assumes a constant hazard over time. Using the exponential distribution would assume a constant HR with other comparators after adjustment with MAICs. As described in Appendix I.5, PH tests after adjustments suggest a violation of the assumption versus comparators.

The Gamma, Gompertz, Generalised gamma and Weibull predict similar hazards to each other, with a slightly increasing hazard after 3 years. The Generalized gamma does not have a good fit in terms of BIC but provides realistic hazards. According to statistical fit and hazard shape, Gamma, Gompertz, Weibull seem to provide the most realistic options and could be considered conservative extrapolation choices.

Figure 43: Progression-free survival (ICR) – smoothed hazards with parametric survival models fit separately to IsaVRd



Abbreviations: Exp, exponential; Gamma, gamma; GG, generalised gamma; Gomp, Gompertz; ICR, independent committee review; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; Llog, log-logistic; Lnor, log-normal; VRd, bortezomib, lenalidomide, and dexamethasone; Weib, Weibull.

External validation

Figure 41 shows that all the models fit the clinical trial data well during the available follow-up, except Log-normal that slightly underestimates survival at the beginning of the follow-up. Table 53 shows that the log-normal and log-logistic models have the highest survival probability at later time points, with 34% and 31% of patients alive and PF at 15 years. The Weibull, Gamma, Gompertz, and Exponential distributions have the lowest and similar survival rates, approximately 40% at 10 years, 25% at 15 years, and 13% at 20 years. These rates are higher than the upper limits of the survival estimates collected during clinician expert interviews, which were 28% (95% CI; 23, 33) at 10 years, 11% (95% CI; 2, 16) at 15 years, and 2% (95% CI; 0, 6) at 20 years.

Therefore, Gamma, Gompertz and Weibull distributions provide the most plausible estimates for IsaVRd PFS. Gamma was chosen in the base case due to a better fit statistic (Table 53).

Table 53: Proportion of patients alive and progression-free at key time points – IsaVRd – adjusted for general population mortality hazards

Distribution	Modelled landmarks			
	5 years	10 years	15 years	20 years
	60 months	120 months	180 months	240 months
Exponential	63.83%	40.74%	25.79%	13.13%
Gamma	63.75%	40.35%	25.31%	12.88%
Generalized gamma	63.79%	40.93%	26.21%	13.34%
Gompertz	63.83%	40.76%	25.81%	13.14%
Log-logistic	64.11%	45.15%	31.10%	15.83%
Log-normal	65.08%	49.52%	34.25%	17.43%

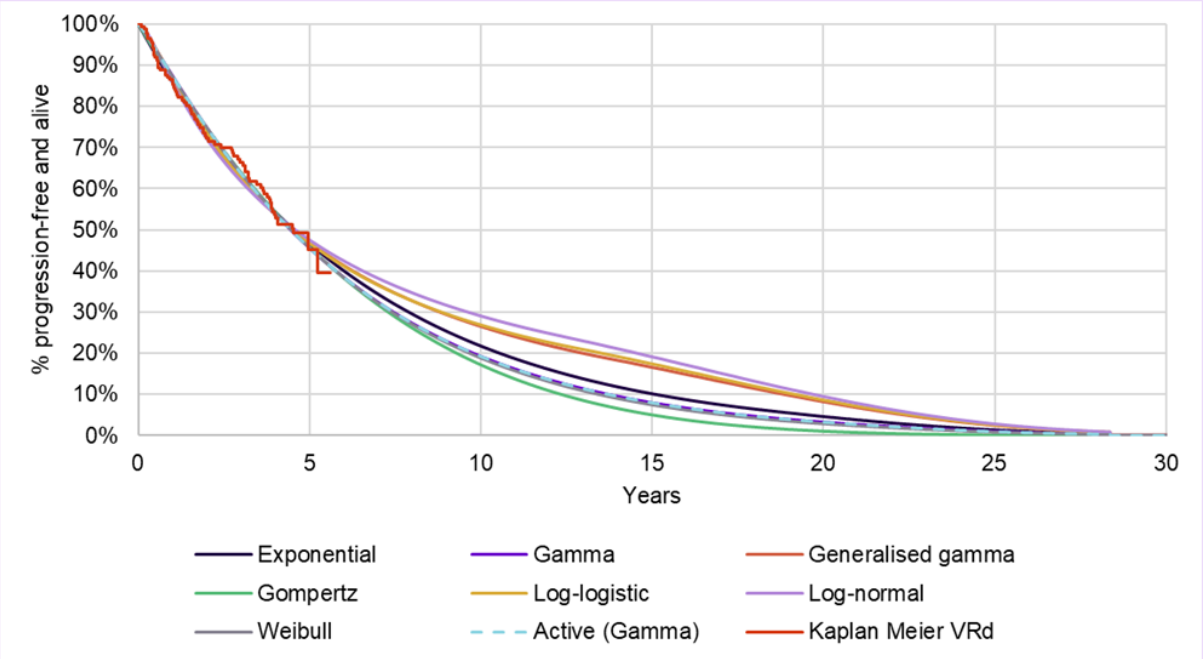
Distribution	Modelled landmarks			
	5 years	10 years	15 years	20 years
	60 months	120 months	180 months	240 months
Weibull	63.75%	40.30%	25.22%	12.84%
IsaVRd – Clinical experts (95%CI)	-	28% (23-33)	11% (2-16)	2% (0-6)

Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone.

B.3.3.2.2 VRd progression-free survival

Parametric models were fit to the IsaVRd arm of the IMROZ study based on the guidance from NICE TSD 14 (130). The Gamma was chosen as the base case extrapolation distribution based on visual inspection on IMROZ follow-up, model fit statistics, smoothed and parametric hazard functions and external validation. PFS VRd extrapolations are presented in Figure 44.

Figure 44: Progression-free survival for VRd (lifetime time horizon – adjusted for general population mortality)

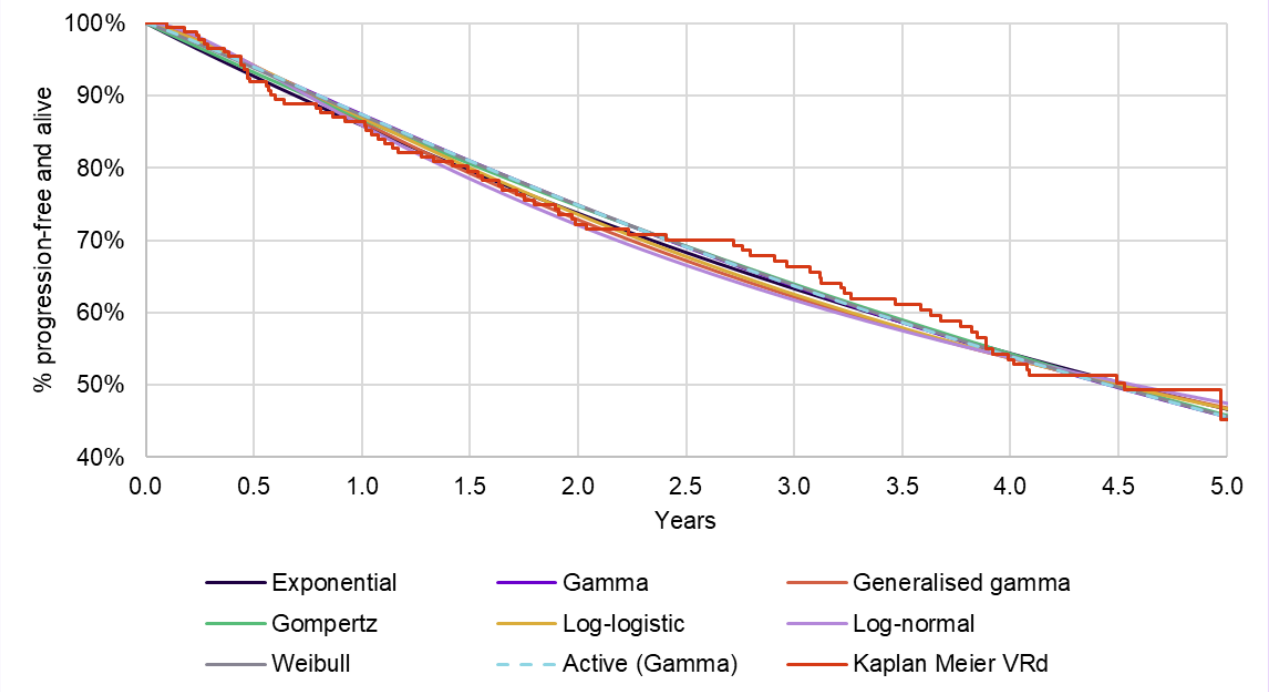


Abbreviations: KM, Kaplan–Meier; VRd, bortezomib, lenalidomide and dexamethasone.

Visual inspection

Figure 45 shows the fit of the different survival models to the VRd IMROZ study data over the period of study follow-up. Visually, all seven models showed a similar fit to the study data during the study period; there was little difference in model fit between the seven distributions.

Figure 45: Progression-free survival for VRd (5-year time horizon) adjusted for general population mortality hazards



Abbreviations: VRd, bortezomib, lenalidomide and dexamethasone.

Internal validation: model fit statistics

The visual fit of the models was consistent with the model comparison statistics shown in Table 54 The AIC statistic for all seven models was within five points of each other, which suggests there is no meaningful difference between models in the goodness of fit to the observed data. For BIC, all were within five points of each other except Log-normal. Overall, according to both AIC and BIC, the Exponential distribution fits best, followed by Log-normal, Gamma, Weibull, Log-logistic and Gompertz.

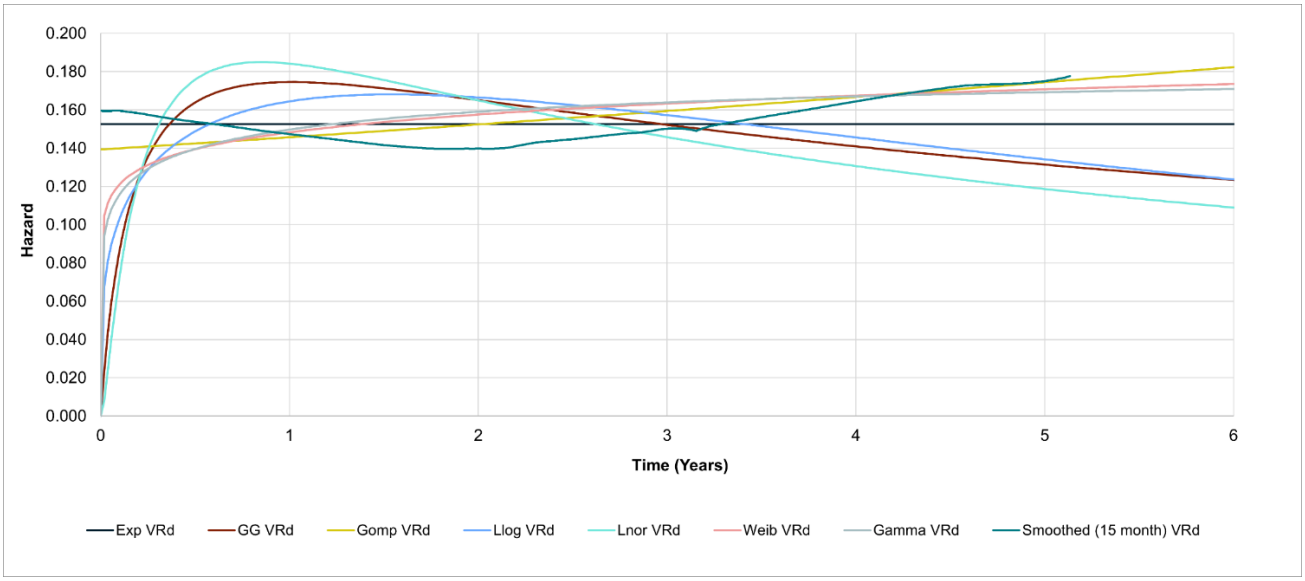
Table 54: Fit statistics of progression-free survival extrapolation – VRd

Distribution	AIC	AIC rank	AIC delta	BIC	BIC rank	BIC delta
Exponential	838.9	1	0.00	842.1	1	0.00
Gamma	840.0	3	1.10	846.4	3	4.34
Generalised gamma	840.8	7	1.93	850.4	7	8.33
Gompertz	840.6	6	1.70	847.0	6	4.90
Log-logistic	840.3	5	1.38	846.6	5	4.58
Log-normal	839.1	2	0.20	845.5	2	3.39
Weibull	840.2	4	1.30	846.6	4	4.50

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival; VRd, bortezomib, lenalidomide and dexamethasone.
Note: AIC and BIC values are rounded to the nearest integer. Cells shaded in yellow are within five points of the best-fitting model.

The smoothed hazard for the VRd arm of the IMROZ study showed that the hazard was constant/slightly increasing (Figure 46). Overlaying the hazards from the parametric survival models with the smoothed hazards observed in IMROZ for VRd suggested that Weibull, Gompertz, Gamma and Exponential distributions fit the VRd data well (Figure 46).

Figure 46: Progression-free survival (ICR) – IMROZ ITT population – smoothed hazards with parametric survival models fit separately to VRd



Abbreviations: Exp, exponential; Gamma, gamma; GG, generalised gamma; Gomp, Gompertz; ICR, independent committee review; ITT, intention-to-treat; IVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; Llog, log-logistic; Lnor, log-normal; VRd, bortezomib, lenalidomide, and dexamethasone; Weib, Weibull.

External validation

Figure 44 shows the extrapolations beyond the end of the trial period up to a lifetime time horizon. Consistent with the OS extrapolations, they are adjusted by age- and gender-matched background mortality calculated using the 2017–2019 ONS life tables for England.(132). Figure 44 indicates that all extrapolations estimate less than 10% PFS by 20 years, with exponential, Gompertz, gamma, and Weibull all displaying the most plausible PFS estimates below 5% at 20 years. The log-normal, log-logistic, and generalized gamma models have the highest PFS probability at later time points, with 19%, 18% and 17% at 15 years and over 5% at 20 years. The distributions have a decreasing hazard, which suggests that these distributions overestimate PFS. The Gompertz distribution shows the lowest survival rates, with approximately 17% at 10 years, 5% at 15 years, and 1% at 20 years. These rates are either at the upper limit or within the confidence interval of the survival estimates gathered from clinician expert interviews, which were 14% (95% CI; 13, 15) at 10 years, 5% (95% CI; 3, 7) at 15 years, and 1% (95% CI; 0, 2) at 20 years. All other distributions have a higher PFS. Therefore, Gompertz provide the most plausible estimates for VRd PFS and was chosen for the scenario with the NMA (Table 55). More information on clinical expert interviews is available in B.3.3.6.

Table 55: Proportion of patients alive and progression-free at key time points – VRd – adjusted for general population mortality hazards

Distribution	Modelled landmarks			
	5 years	10 years	15 years	20 years
	60 months	120 months	180 months	240 months
Exponential	46.74%	21.84%	10.15%	4.66%
Gamma	45.71%	19.35%	7.99%	3.29%
Generalised gamma	46.96%	26.55%	16.61%	8.45%
Gompertz	45.92%	17.35%	5.08%	1.10%
Log-logistic	46.83%	26.90%	17.50%	8.91%
Log-normal	47.57%	29.07%	19.27%	9.81%
Weibull	45.75%	18.97%	7.49%	2.90%
IsaVRd – Clinical experts (95%CI)	-	14% (13-15)	5% (3-7)	1% (0-2)

Abbreviations: CI, confidence interval, IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone.

B.3.3.2.3 Comparators not included in IMROZ

Justification for time-varying HR

PH assumption was tested between IsaVRd and comparators after matching. Diagnostic tests indicate that PH does not hold between IsaVRd and all other comparators. Full details are presented in Appendix I.5. Therefore, an approach that relaxes the PH assumption is preferred and used in the base-case. Constant HR MAICs and IPW will be tested in a scenario analysis.

In line with overall survival, the same distribution was used to estimate time-varying HR after matching and for the IsaVRd distribution in the model. Therefore, for PFS, Gamma distribution is used. The time-varying HRs for Gamma are presented in Table 56. HRs for progression-free survival are presented at various time points, comparing IsaVRd with DRd, Rd, VMP, and VCd. Values are less than 1 and suggest a survival benefit for IsaVRd compared to the comparators. The different HRs suggest an improving treatment effect over time of IsaVRd versus all comparators. The time-varying HRs between IsaVRd and DRd, Rd, VMP, and VCd for all distributions are described in Appendix I.5.3. Fit statistics for IsaVRd after matching are presented in Appendix I.5.1.

Table 56: Landmark HRs for progression-free survival – Gamma distribution

Time (years)	HR (95% CI) for IsaVRd versus comparators			
	DRd	Rd	VMP	VCd
1	[redacted]	[redacted]	0.21 (0.15, 0.29)	0.35 (0.25, 0.47)
2	[redacted]	[redacted]	0.18 (0.13, 0.26)	0.33 (0.24, 0.45)
5	[redacted]	[redacted]	0.16 (0.11, 0.26)	0.32 (0.21, 0.48)
5.67*	[redacted]	[redacted]	0.16 (0.11, 0.26)	0.32 (0.21, 0.48)
10	[redacted]	[redacted]	0.15 (0.10, 0.26)	0.31 (0.20, 0.50)
28	[redacted]	[redacted]	0.14 (0.08, 0.27)	0.31 (0.18, 0.52)

Abbreviations: CI, confidence interval; DRd, daratumumab, lenalidomide, and dexamethasone; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone.
* End of IMROZ follow-up

Final progression-free survival for IsaVRd and all comparators is described in Figure 47. IsaVRd demonstrated a better PFS benefit than all comparators, and is followed by DRd, Rd, VCd and VMP.

Figure 47: Progression-free survival for IsaVRd, DRd, Rd, VMP, and VCd (lifetime time horizon – adjusted for general population mortality)

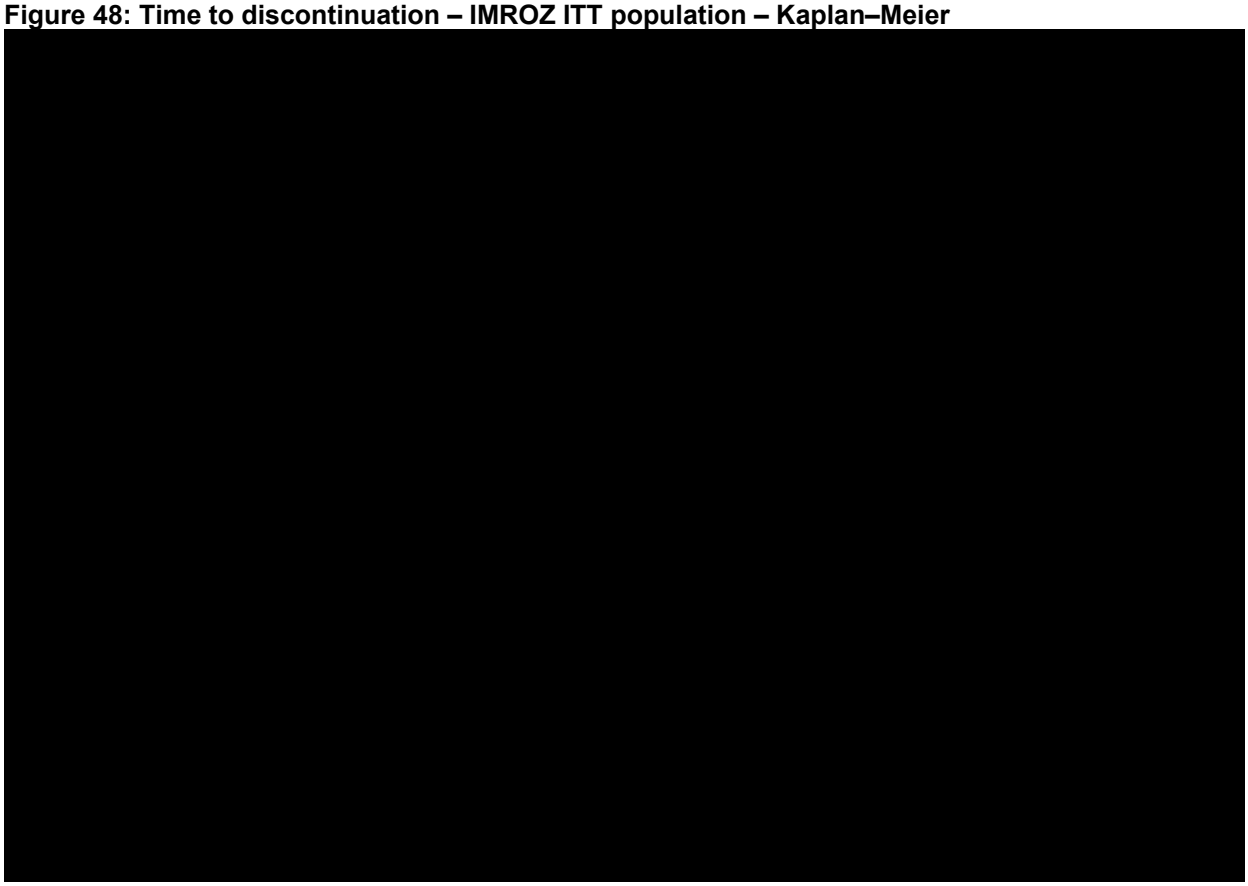
A: IsaVRd vs DRd; B: IsaVRd vs Rd; C: IsaVRd vs VMP; D: IsaVRd vs VCd.
Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; KM, Kaplan-Meier; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; Rd, lenalidomide and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

B.3.3.3 *Time to treatment discontinuation (TTD) extrapolation*

In line with overall survival and progression-free survival, parametric models were fit separately to each arm of the IMROZ trial. This approach follows the guidance from NICE TSD 14, which states that PH assumption is unnecessary when patient-level data are available (130).

The Kaplan-Meier data for IsaVRd and VRd are presented in Figure 48. IsaVRd showed longer TTD than VRd with an increasing gap over time. Confidence interval crosses until month 18.

Figure 48: Time to discontinuation – IMROZ ITT population – Kaplan–Meier



Abbreviations: IVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone.

B.3.3.3.1 IsaVRd

Extrapolation of TTD

Parametric models were fit to the IsaVRd arm of the IMROZ study based on the guidance from NICE TSD 14 (130).

The exponential, Generalised gamma and Gamma distributions provide a suitable fit to the TTD data for the IsaVRd arm of IMROZ based on visual inspection on IMROZ follow-up, model fit statistics and smoothed and parametric hazard functions. IsaVRd extrapolations are presented in Figure 49. The log-normal and log-logistic models have the highest survival probability at later time points. The Generalised Gamma, Exponential and Gamma distributions have the lowest survival probability. The exponential model was preferred because it has the lowest overall AIC of the

acceptable curves, the extrapolated hazards for each acceptable distribution are approximately constant, the exponential does not appear to either under- or over-predict TTD for IsaVRd.

Figure 49: Time to treatment discontinuation IsaVRd (life time horizon) adjusted by PFS

Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone.

Visual Inspection

The range of parametric model fits to TTD Kaplan–Meier data is shown in Figure 50. Visually, all seven provide a good fit over the IMROZ clinical study period except the Log-normal.

Figure 50: Time to treatment discontinuation IsaVRd (5-year time horizon)

Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone.

Model fit statistics

AIC and BIC values are provided for the standard parametric curves in Table 57. For AIC, all models, except Log-normal, are within five points of each other, indicating that there is little meaningful difference between the remaining models regarding the goodness of fit to the observed data. For BIC, Exponential, Gamma and Weibull fit better than the other models. Gompertz is within six points of the best fitting model. Log-logistic, Generalised gamma and Log-normal do not fit well with more than seven, nine and thirteen points from the best fitting model. Overall, according to both AIC and BIC, the Exponential distribution fits best, followed by Gamma and Weibull.

Table 57: Time to treatment discontinuation fit statistics of extrapolation – IsaVRd

Distribution	AIC	AIC rank	AIC delta	BIC	BIC rank	BIC delta
Exponential	1484.3	1	0.0	1487.9	1	0.0
Gamma	1485.0	2	0.7	1492.1	2	4.3
Generalised gamma	1486.7	5	2.4	1497.4	6	9.5
Gompertz	1486.0	4	1.7	1493.2	4	5.3
Log-logistic	1488.4	6	4.1	1495.5	5	7.6
Log-normal	1494.2	7	9.9	1501.3	7	13.5
Weibull	1485.1	3	0.8	1492.3	3	4.4

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.
Notes: AIC and BIC values are rounded to the nearest integer. Cells shaded in yellow are within five points of the best fitting model. Cells shaded in blue are within five points of the second-best-fitting model.

Smoothed and parametric hazards

As shown in Figure 51, Generalised gamma describes a decreasing and increasing hazard over time, with the higher hazard at the end of the trial follow-up among all other distributions, followed by exponential that describes a constant hazard. This is followed by Gamma, Gompertz Weibull which have a very similar and decreasing hazard. Then Log-normal and Log logistic describe an increasing and decreasing hazard over time with the lowest hazard at the end of the lowest hazard at the end of the trial follow-up. The smoothed hazard plot for IsaVRd indicates that the hazard is approximately constant, suggesting an exponential distribution would fit well. Following the same reasoning than for PFS, a decreasing hazard over time is implausible. As a result, the Log-normal, Log logistic, Gamma and Weibull would not be realistic. According to statistical fit and hazard shape, Exponential and Generalized gamma seem to provide the most realistic options.

Figure 51: Time to discontinuation – IMROZ ITT population – smoothed hazards with parametric survival models fitted separately to IsaVRd

Abbreviations: Exp, exponential; Gamma, gamma; GG, generalised gamma; Gomp, Gompertz; ITT, intention-to-treat; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; Llog, log-logistic; Lnor, log-normal; VRd, bortezomib, lenalidomide, and dexamethasone; Weib, Weibull.

External validation

Figure 49 shows that all of the extrapolation distribution models fit the clinical trial data well during the available follow-up except for Log-normal. Table 58 shows that the log-normal and log-logistic models have the highest survival probability at later time points, [redacted]. The Generalised Gamma, Exponential and Gamma distributions have the lowest survival probability. The TTD was capped by PFS. No additional external validation could be performed. Therefore, due statistical fit, the Exponential distribution was chosen for the base-case.

Table 58: Proportion of patients alive and on treatment at key time points – IsaVRd (after adjustment for PFS)

Distribution	Modelled landmarks			
	5 years	10 years	15 years	20 years
	60 months	120 months	180 months	240 months
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; PFS, progression-free survival.

B.3.3.3.2 Comparators not included in IMROZ

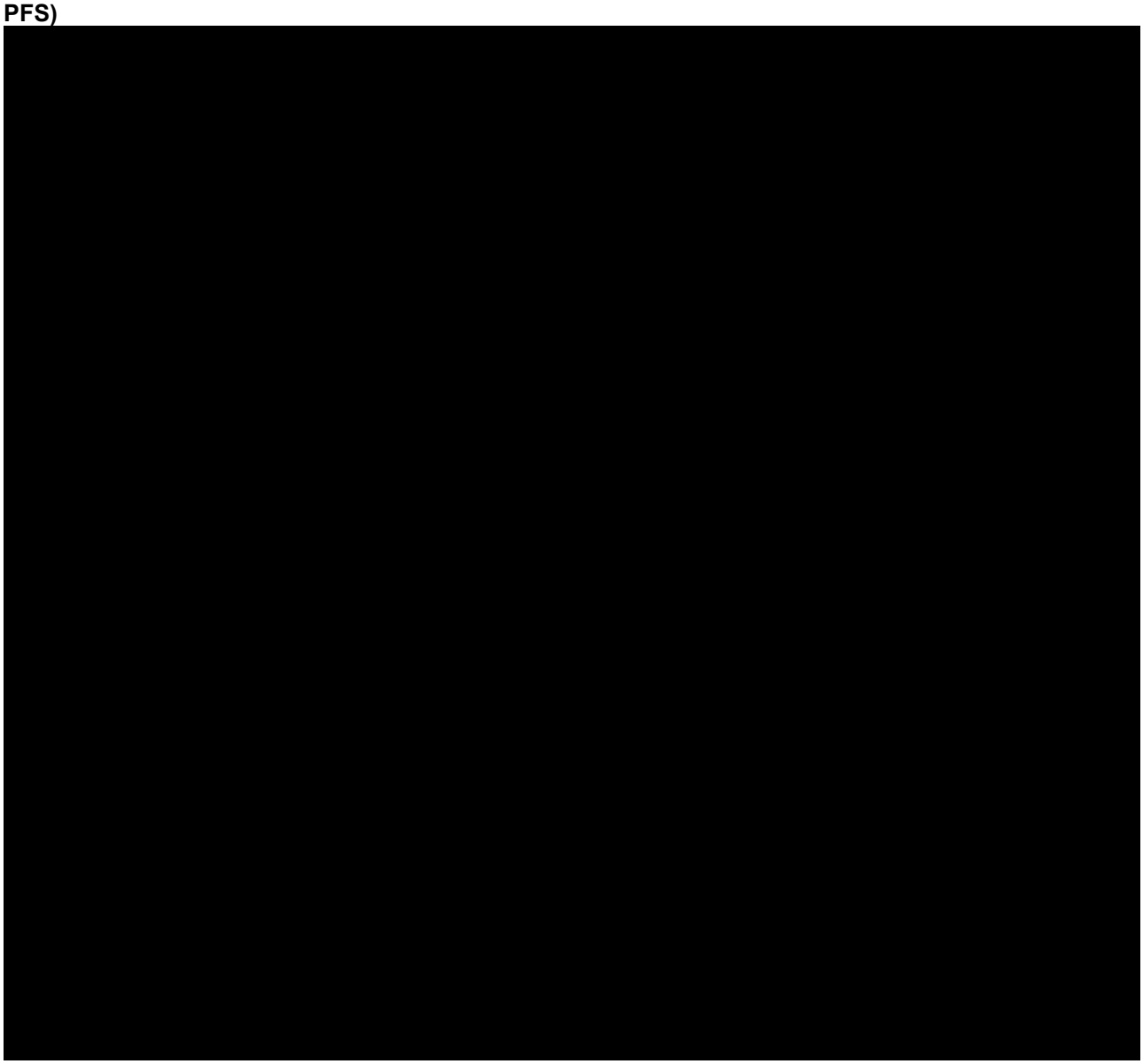
For comparators not included in the IMROZ trial, the time to discontinuation (TTD) is not usually publicly available and is redacted heavily in HTA. However, for DRd, the TTD curve is available and a MAIC was conducted to estimate the comparative efficacy between IsaVRd and DRd TTD using IMROZ and MAIA. PH assumption was tested between IsaVRd and DRd after matching. The results show no difference in TTD curves [redacted], indicating that there is no evidence of a time-varying HR. Diagnostic tests are presented for completeness in Appendix I.5. Therefore, the base-case for DRd will use constant HR MAIC. The use of a MAIC is in line with the methodology used to model OS and PFS. A scenario with a HR of 1.00 will be tested in a scenario analysis.

Two alternative approaches for modelling DRd TTD were tested in scenario analyses. The first approach involves applying a TTD vs PFS time-varying hazard ratio from MAIA to the DRd PFS from the ITC. The time-varying HR was estimated using the committee's preferred assumption for TTD in TA917 (Gompertz distribution) and the PFS distribution in the IsaVRd cost-effectiveness analysis (Gamma distribution). This method is not considered robust because it assumes that the time-varying hazard ratios between treatments are consistent and unaffected by differences in patient baseline characteristics. This assumption is further invalidated as differences in patient population have been shown to influence PFS and OS for DRd before and after matching. The second approach involves using the MAIA DRd TTD KM. This approach leads to a naïve comparison between IMROZ and MAIA which is inconsistent with the comparison for PFS and OS where relative efficacy was estimated. Additionally, after adjusting for differences in baseline characteristics, it appears that there is limited evidence of a difference in TTD between IsaVRd and DRd.

Alternative sources to calculate TTD are needed for other comparators not included in IMROZ. Evidence on median duration of treatment (DoT), which is more often reported in pivotal trial publications than TTD, was leveraged. Of note, both DoT and TTD are comparable metrics used in healthcare to evaluate how long patients continue a specific treatment before discontinuing it. Both metrics are valuable for understanding patient adherence and treatment persistence. However, the key difference between the two measures is that TTD is a time to event outcome while median DoT is not, and therefore DoT does not consider censoring. In the absence of TTD, the median DoT could be considered a proxy for median TTD as long as the trial follow-up is longer than the median TTD and there is little censoring. A HR is derived using the median PFS and the median DoT and applied to PFS from the ITC to calculate a TTD curve. This is further explained in Appendix I.5.5.2. This approach is considered the most accurate one as it uses reported duration of treatment. Limitations associated to this method are not considered impactful given the small cost of Rd, VMP and VCd. Additionally, VMP and VCd costs are capped by a stopping rule as described in the following section.

Time-on-treatment for IsaVRd and all comparators is shown in Figure 52. IsaVRd demonstrated a similar time-on-treatment than DRd, and is followed by Rd, VCd and VMP.

Figure 52: Time-on-treatment for IsaVRd, DRd, Rd, VMP, and VCd (lifetime time horizon – adjusted for PFS)



A: IsaVRd vs DRd; B: IsaVRd vs Rd; C: IsaVRd vs VMP; D: IsaVRd vs VCd.
Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; KM, Kaplan-Meier; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; Rd, lenalidomide and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

B.3.3.3.3 Stopping rules

Stopping rules are common practice in oncology treatment. If an intervention has a stopping rule, patients can only receive it for a stipulated number of cycles. Some treatments have stopping rules in their marketing licence that cover all reimbursement agencies; other treatments have been approved by an HTA body with an imposed stopping rule.

Within the cost-effectiveness model, stopping rules are applied to a variety of comparators. A stopping rule after a set number of weeks is applied to:

- VCd at 24 weeks (133)
- VMP at 54 weeks (127)

No stopping rules are applied to IsaVRd in IMROZ in line with recommended dosing.

B.3.3.4 *General population mortality*

The model includes general population mortality matched by age and gender information from the 2017–2019 Office for National Statistics life tables for England (116). The decision to use this publication over more recent data years stems from the latest releases potentially incorporating biases from COVID-19; this choice also aligns with the latest guidance from TSD 23 (131), which encourages models to 'use figures from the three-year band 2017 – 2019'. To ensure that OS predicted by the model for each treatment did not exceed that of the general population, age- and gender-matched general population mortality was used in any cycle where the predicted rate of death was lower than general population mortality.

B.3.3.5 *Adverse events*

The incidence of AEs associated with IsaVRd and VRd was informed by IMROZ, whereas other comparators were informed by relevant trials. The cost-effectiveness model considered AEs of Grade 3 or higher with an incidence of 5% or more across pivotal trials; this resulted in 19 AEs being specified. This approach aligned with recent NICE submissions (e.g., TA917 (72)) and followed the assumption that AEs of a lower grade or proportion would have a negligible impact on the average patient's cost burden and quality of life. The approach also assumed a 5% threshold would capture AEs that would likely affect patients in a real-world environment where AEs are not monitored as strictly as in a clinical trial. AE rates were informed by the number of patients experiencing each specific event, which was converted to a percentage based on the number of patients in the associated trial (Table 59).

Table 59. Number (incidence) of AE events (Grade 3 or higher with an incidence of 5%)

Adverse event	IsaVRd	DRd	Rd	VMP	VCd
Number of patients	*263*	*364*	*365*	*340*	*340*
Neutropenia	79 (30.04%)	197 (54.12%)	135 (36.99%)	136 (40.00%)	136 (40.00%)
Anaemia	0 (0.00%)	61 (16.76%)	79 (21.64%)	62 (18.24%)	62 (18.24%)
Lymphopenia	0 (0.00%)	60 (16.48%)	41 (11.23%)	67 (19.71%)	67 (19.71%)
Leukopenia	0 (0.00%)	42 (11.54%)	23 (6.30%)	77 (22.65%)	77 (22.65%)
Thrombocytopenia	31 (11.79%)	32 (8.79%)	34 (9.32%)	126 (37.06%)	126 (37.06%)
Pneumonia	53 (20.15%)	70 (19.23%)	39 (10.68%)	22 (6.47%)	22 (6.47%)
Hypokalaemia	0 (0.00%)	46 (12.64%)	36 (9.86%)	22 (6.47%)	22 (6.47%)
Cataract	41 (15.59%)	40 (10.99%)	39 (10.68%)	0 (0.00%)	0 (0.00%)
Diarrhoea	20 (7.60%)	32 (8.79%)	22 (6.03%)	25 (7.35%)	25 (7.35%)
Fatigue	21 (7.98%)	32 (8.79%)	17 (0.00%)	25 (7.35%)	25 (7.35%)
Hypertension	0 (0.00%)	31 (8.52%)	16 (0.00%)	0 (0.00%)	0 (0.00%)
Hyperglycaemia	0 (0.00%)	28 (7.69%)	14 (0.00%)	0 (0.00%)	0 (0.00%)
Pulmonary embolism	13 (0.00%)	26 (7.14%)	19 (5.21%)	0 (0.00%)	0 (0.00%)
Asthenia	7 (0.00%)	19 (5.22%)	17 (0.00%)	21 (6.18%)	21 (6.18%)
Acute Kidney injury	0 (0.00%)	19 (5.22%)	12 (0.00%)	0 (0.00%)	0 (0.00%)
Chronic kidney disease	0 (0.00%)	0 (5.22%)	10 (0.00%)	0 (0.00%)	0 (0.00%)
Peripheral sensory neuropathy	19 (7.22%)	0 (0.00%)	0 (0.00%)	44 (12.94%)	44 (12.94%)
Syncope	15 (5.70%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Covid-19 pneumonia	21 (7.98%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Adverse event	IsaVRd	DRd	Rd	VMP	VCd
Source	IMROZ CSR (134) (Table 57)	Orlowski et al. 2021 (135) (MAIA, DRd)	Orlowski et al. 2021 (135)	San Miguel 2008 (82) (VISTA)	Assumed equal to VMP

Note: For AEs with an incidence rate less than 5%, the number of events is set to 0.

Abbreviations: AE, adverse event; CSR, clinical study report; DRd, daratumumab, lenalidomide and dexamethasone; Rd, lenalidomide and dexamethasone; VCd, bortezomib, cyclophosphamide and dexamethasone; VMP, bortezomib, melphalan and prednisone; VRd, bortezomib, lenalidomide and dexamethasone; VTd, bortezomib, thalidomide and dexamethasone.

B.3.3.6 *Clinical expert assessment of applicability of clinical parameters*

Clinician expert validation interviews were conducted to elicit OS and PFS estimates for IsaVRd and VRd (136).

B.3.4 *Measurement and valuation of health effects*

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

Five-level EQ-5D™ (EQ-5D-5L) data were collected in the IMROZ clinical trial (refer to Section B.2.6.1.6).

In the IMROZ clinical trial, the EQ-5D questionnaire was administered to patients during assessments at each visit. More specifically, the EQ-5D-5L questionnaire was provided to patients on Day 1 of Cycle 1 and Day 1 of Cycles 2–4 in the induction phase in which one cycle lasted 6 weeks and in the continuous phase, the questionnaire was provided to patients on Day 1 of Cycles >4 in which cycles lasted 4 weeks. The questionnaire was also provided to patients at the end of treatment (Day 30 following the last investigational medicinal product [IMP] administration) and at 90 days post-treatment (123).

B.3.4.2 *Mapping*

EQ-5D-5L responses from IMROZ were mapped to the EQ-5D-3L using the Hernández Alava mapping method in accordance with the NICE guidance for estimates for the UK (137). The mapped responses were then used within a standard regression equation to identify significant factors that influence utility as described in Section B.3.4.6.

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

An SLR was conducted (finalised in January 2023) to identify the humanistic impact of disease and treatment of NDMM in terms of HRQoL and utilities. This report was updated on 29 April 2024.

Electronic databases were searched on 14 November 2022 and updated on 29 April 2024 via the OvidSP platform to identify peer-reviewed studies of interest. The databases searched included:

- Embase
- MEDLINE and MEDLINE In-Process
- EconLit
- CENTRAL
- Cochrane Database of Systematic reviews
- HTA Database
- National Health Service Economic Evaluation Database

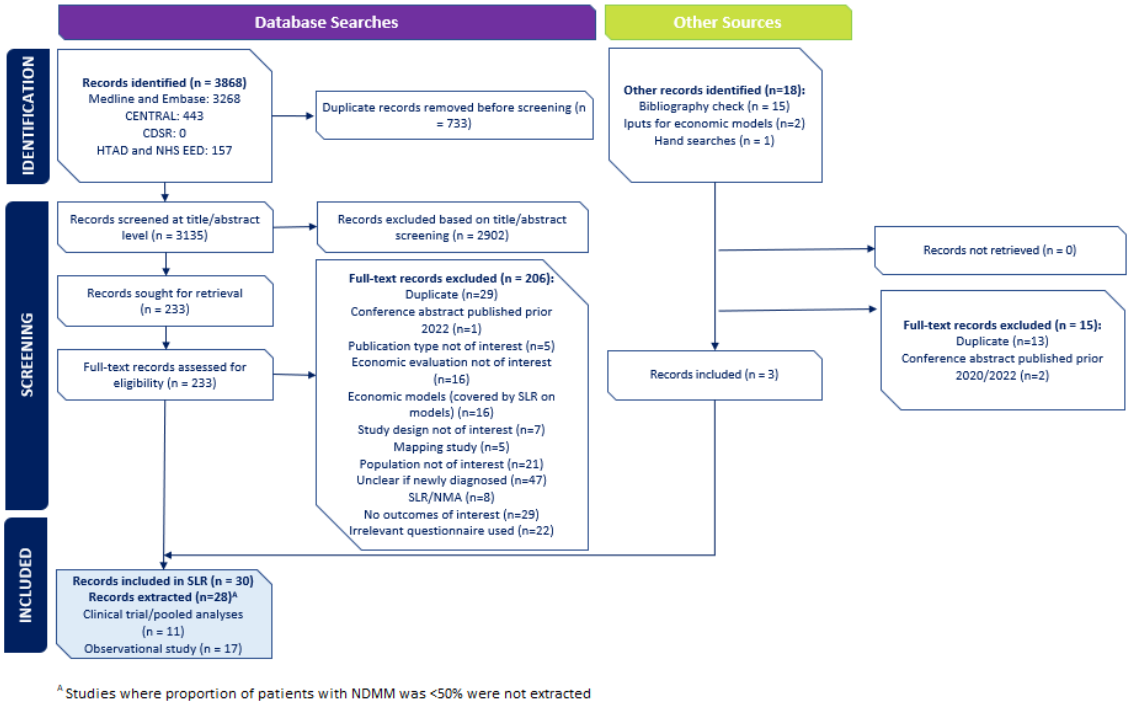
Additional searches were conducted in conference proceedings, HTA websites and databases, and bibliographies of relevant SLRs published since 2016 to identify any publication not identified

in the electronic database search phase. Full details of the searches and results for economic evaluation studies identified are reported in Appendix H.

In the updated SLR (April 2024), systematic searches for the humanistic burden yielded a total of 3,868 records from electronic literature databases. After the removal of duplicate references, 3,135 records were screened at the title and abstract level. Of these, 233 publications were eligible for screening at the full-text level, from which 27 publications were included. In addition, three relevant records were identified during the grey literature searches. Hence, a total of 30 records were included for final review.

The PRISMA flow diagram for the updated search (April 2024) is presented in Figure 53.

Figure 53: PRISMA diagram for humanistic evaluations (April 2024)



Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; HTAD, Health Technology Assessment Database; NDMM, newly diagnosed multiple myeloma; NHS EED, National Health Service Economic Evaluation Database; NMA, network meta-analyses; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; SLR, systematic literature review.
Source: Economic and Humanistic SLR update (106).

B.3.4.4 *Key differences*

The economic and humanistic SLR identified three studies measuring utilities in transplant-ineligible patients with NDMM using the EQ-5D questionnaire (Appendix H.2.1.1.2). All identified studies in the SLR reported utility values that either used a non-UK value set, were derived from a non-UK population, or had not been cross-walked using Hernández Alava et al. (2017) (118), in line with the NICE reference case, and therefore were not considered relevant to this submission. In the model, both data from literature and clinical trials were used.

Two literature sources to inform health-state utility values are included in the model (Table 60).

- **TA587** – Utilities from the VISTA trial for the PFS health state and from the FIRST trial for the PPS health state were reported inTA587 (73). The VISTA trial reported EQ-5D-3L

utilities by cycle up to week 32, with a single value reported for the period after Week 32. For simplicity, a mean utility value was reported for the period before 32 weeks.

- **Hatswell et al. 2019** – Hatswell et al. conducted a meta-regression and presented health state utilities in multiple myeloma (138). It was assumed that the progression-free health state was informed by the utility reported for 1st line, and progressed disease was informed by the utility reported for 2nd line.

Table 60: Literature health state utility values

Source	Health status	Mean utility	Standard error (SE)†
VISTA trial (TA587)	Progression-free (first 32 weeks)	0.549	0.055
	Progression-free (post 32 weeks)	0.632	0.063
FIRST trial (TA587)	Progressed	0.557	0.056
Hatswell et al. 2019	Pre-progression	0.620	0.062
	Post-progression	0.590	0.059

† SE is assumed to be 10% of the mean input value.
Abbreviation: SE, standard error.

B.3.4.5 *Adverse reactions*

QALY losses from AEs were calculated by multiplying the rate of Grade 3/4 AEs for each treatment regimen based on IMROZ and comparator trials with the associated utility decrement and AE duration (Table 61). It was assumed that the same utility decrement and duration per event should be applied to all patients regardless of which treatment they receive. The resulting event utility was deducted from patients' pre-progression health state utility. This approach and the utility decrements were based on published literature and aligned with TA917, following the same assumptions.

Table 61: Disutility and duration of adverse events

Adverse event	Event utility decrement	Event duration (days)	Total event utility	Source (utility decrement and duration)
Neutropenia	-0.150	7.0	-0.003	TA917 (72)
Anaemia	-0.310	180.0	-0.153	
Lymphopenia	-0.070	15.5	-0.003	
Leukopenia	-0.070	14.7	-0.003	
Thrombocytopenia	-0.310	7.0	-0.006	
Pneumonia	-0.190	7.0	-0.004	
Hypokalaemia	-0.070	11.4	-0.002	
Cataract	-0.010	28.0	-0.001	
Diarrhoea	-0.100	12.0	-0.003	

Adverse event	Event utility decrement	Event duration (days)	Total event utility	Source (utility decrement and duration)
Fatigue	-0.120	14.6	-0.005	
Hypertension	-0.150	11.4	-0.005	
Hyperglycaemia	-0.150	14.7	-0.006	
Pulmonary embolism	-0.310	7.0	-0.006	
Asthenia	-0.120	14.6	-0.005	
Acute Kidney injury	-0.180	7.0	-0.003	
Chronic kidney disease	-0.050	365.3	-0.050	
Peripheral sensory neuropathy	-0.020	50.0	-0.002	TA870 (109)
Syncope	0.000	14.0	0.000	TA970 (139)
Covid-19 pneumonia	-0.190	7.0	-0.033	Assumed to be equal to pneumonia

Abbreviations: Covid-19, coronavirus disease 2019; DRd, daratumumab, lenalidomide, and dexamethasone; Sd, selinexor and dexamethasone; TA, technology assessment.

B.3.4.6 *Health-related quality-of-life data used in cost-effectiveness analysis*

EQ-5D-5L data were collected in the IMROZ clinical trial. According to NICE methods manual, three-level EQ-5D (EQ-5D-3L) is the preferred utility measure (117). Therefore, the EQ-5D-5L responses were mapped to the EQ-5D-3L using the Hernández Alava mapping method in accordance with the NICE guidance for estimates for the UK (140).

Statistical utility analysis was conducted to determine the utility regressions informing health state utility values by treatment. Mixed-effect repeated measure regression models (MMRMs) were used to estimate the average utility value in each health state for each treatment after adjusting for prognostic factors and multiple observations from a given patient. Several covariates were identified that could influenced the utility value. These baseline variables were chosen from sources including the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 12 (141), the IMROZ CSR, and clinical input from interviews (100), aligning with variables considered clinically relevant for inclusion in the Inverse Probability of Censoring Weights (IPCW) adjustment for crossover in IMROZ.

To understand the relationship between utility and these variables, univariate models were fitted. Variables that were significant at the 20% level were included in the saturated model. For the variables identified as significant by the univariate models, bivariate models with a treatment interaction term were fitted to assess the relationship between treatment and each significant variable. Variables tested for inclusion in the saturated model are presented in Table 106 in Appendix I.6. Stepwise selection was then applied to fit the chosen model.

Three utility regression models are presented in the cost-effectiveness model. The justification for the base case selection is detailed below:

- Model 1: Model using stepwise selection
- Model 2: Model with overall response (OR) removed (base-case)
- Model 3: Model with OR and treatment removed

The coefficients and utility estimates for each model are detailed in Table 62 and Table 63.

Model using stepwise selection

In the cost-effectiveness model, utility was adjusted due to the effects of age and gender, as recommended by NICE DSU TSD12 (141). A health state variable is also essential to estimating pre- and post-progression utility, therefore progression status was held in the utility models. Interaction terms between each significant variable and treatment were also tested. ECOG PS and OR were included in all the utility models because both variables had significant effect on utility in univariate models as well as a significant treatment interaction at the 20% level in the bivariate models. It is intuitive to think that patients with worse ECOG performance at baseline could have lower quality of life as they might be considered more unwell. Similarly, patients with lower OR would likely have lower quality of life as they might be considered more unwell. Additionally, since IMROZ was an open-label trial, the difference in utility between treatment arms at baseline may be due to the perceived benefit of IsaVRd being a new and potentially more effective treatment. Therefore, baseline utility was held in the models to rebalance the utility observations at a common baseline across treatments.

Stepwise selection was optimised by AIC. The stepwise selected model for was defined as:

$$\begin{aligned}\text{Utility}_i = {} & \beta_0 + \beta_1 \times \text{Baseline utility} + \beta_2 \times \text{Age} + \beta_3 \times \text{Sex} + \beta_4 \times \text{Progression status} \\ & + \beta_5 \times \text{ECOG PS} + \beta_6 \times \text{Treatment} + \beta_7 \times \text{OR} + \beta_8 \times \text{Sex} \times \text{Treatment} \\ & + \beta_9 \times \text{ECOG PS} \times \text{Treatment} + \beta_{10} \times \text{OR} \times \text{Treatment} + \epsilon_i\end{aligned}$$

where the β values are the regression coefficients and ϵ_i is the random intercept per subject.

When IRC assessment was used, the coefficient for progression status was -0.001, suggesting lower utility for progressed patients. The coefficient for OR was 0.001, indicating that patients with a weaker response than partial response (PR) had a higher utility. When investigator assessment was used, the coefficients for OR and progression were negative, meaning patients with progressed disease were expected to have lower utility than those prior to progression, and patients with worse response than PR were expected to have lower utility than those with better response than PR. Counterintuitive results with the model using IRC assessment could be prevented if investigator assessment was used instead, in which the coefficients for progression and OR were negative. Additionally, the difference in utility estimates was almost negligible for the pre-progression state between the models using IRC and investigator assessments. Therefore, the models using investigator assessment may be more suitable to estimate utility, especially for the pre-progression state. However, the differences between pre- and post-progression were small for all models, which was counterintuitive clinically and inconsistent with published literature.

Additionally, the coefficients of IsaVRd (treatment covariate) was 0.06 in the model and was statistically significant, suggesting improved utility for IsaVRd patients.

Model using stepwise selection without OR

The model using stepwise selection resulted in poorly estimated PP; the difference between PF and PP health states is not considered a realistic estimation of PP utility when compared with the literature. A potential cause for this is the relationship between progression status and OR. Indeed, progressed disease was part of the OR measurement, which could violate the uncorrelated requirement between covariates. In this model, the impact of the relationship between progression status and OR on health state utility estimation is investigated by removing OR from the utility models.

When OR is removed, the utility model is defined as:

$$\text{Utility}_i = \beta_0 + \beta_1 \times \text{Baseline utility} + \beta_2 \times \text{Age} + \beta_3 \times \text{Sex} + \beta_4 \times \text{Progression status} + \beta_5 \times \text{ECOG PS} + \beta_6 \times \text{Treatment} + \beta_7 \times \text{Sex} \times \text{Treatment} + \beta_8 \times \text{ECOG PS} \times \text{Treatment} + \epsilon_i$$

The utility decrement was larger for the models using investigator assessment for progression. The post-progression utility was estimated to reduce by 0.005 when using the IRC definition of progression (versus 0.001 in model with OR; Table 62) and 0.018 when using the investigator definition of progression (versus 0.007 in model with OR; Table 62). The pooled utility estimates for the pre-progression state were identical to those from Model 1 (Table 63). The pooled utilities for the post-progression state were 0.708 using the IRC assessment and 0.695 using the investigator assessment. The results suggest inclusion of OR as a covariate impacted the estimation of the utility decrement for the post-progression health state.

Additionally, the coefficient of IsaVRd (treatment covariate) was still 0.06 in the model and was still statistically significant, suggesting improved utility for IsaVRd patients versus VRd.

Model using stepwise selection without OR and treatment

This model explores the impact of removing OR and treatment from the utility regression. Removing OR improved the estimation of health state utilities for the models, whether progression status was assessed by ICR or investigator assessment, verifying the relationship between progression and response.

When treatment is removed from the model, the UK model reduces to:

$$\text{Utility}_i = \beta_0 + \beta_1 \times \text{Baseline utility} + \beta_2 \times \text{Age} + \beta_3 \times \text{Sex} + \beta_4 \times \text{Progression status} + \beta_5 \times \text{ECOG PS} + \epsilon_i$$

Table 62: Parameters estimates from Model 1, 2 and 3, and associated p-value

	Model 1: Stepwise Selected (p-value)		Model 2: Without OR (p-value)		Model 3: Without OR and Treatment (p-value)	
Covariate	**IRC**	**INV**	**IRC**	**INV**	**(IRC**	**INV**
Intercept	0.786 (< 0.001)	0.789 (< 0.001)	0.787 (< 0.001)	0.787 (< 0.001)	0.817	0.816
Baseline Utility	0.385 (< 0.001)	0.384 (< 0.001)	0.385 (< 0.001)	0.384 (< 0.001)	0.371	0.371
Age	-0.005 (0.004)	-0.005 (0.004)	-0.005 (0.004)	-0.005 (0.004)	-0.005	-0.005
Sex (ref: male)	0.044 (0.072)	0.043 (0.079)	0.044 (0.072)	0.043 (0.079)	-0.009	-0.009
Progression Status (ref: not progressed)	-0.001 (0.909)	-0.007 (0.470)	-0.005 (0.539)	-0.018 (0.038)	-0.005	-0.019
ECOG PS (ref: ≤1)	-0.086 (0.038)	-0.083 (0.043)	-0.086 (0.038)	-0.086 (0.037)	0.001	0.001
Treatment (ref: VRd)	0.064 (0.004)	0.060 (0.007)	0.063 (0.005)	0.062 (0.005)	-	-
OR (ref: PR or greater)	0.001 (0.952)	-0.020 (0.025)	-	-	-	-
Sex × Treatment	-0.086 (0.007)	-0.085 (0.007)	-0.087 (0.006)	-0.086 (0.007)	-	-

	Model 1: Stepwise Selected (p-value)		Model 2: Without OR (p-value)		Model 3: Without OR and Treatment (p-value)	
Covariate	**IRC**	**INV**	**IRC**	**INV**	**(IRC**	**INV**
ECOG PS × Treatment	0.165 (0.002)	0.162 (0.002)	0.165 (0.002)	0.165 (0.002)	-	-
OR × Treatment	-0.016 (0.183)	0.017 (0.129)	-	-	-	-

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICR, Independent Central Review; INV, Investigator; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; OR: overall response, PFS, progression-free survival; PPS, post-progression survival; PR, partial response; VRd: bortezomib, lenalidomide, and dexamethasone.

Table 63: Utility values from Models 1, 2 and 3

Model	Progre-ssion status	ICR/ INV	Utility (95% CI)		
			Pooled	IsaVRd	VRd
Model 1: Stepwise Selected	PFS	ICR	0.712 (0.696, 0.727)	0.728 (0.708, 0.748)	0.688 (0.664, 0.711)
		INV	0.713 (0.697, 0.727)	0.728 (0.708, 0.748)	0.688 (0.664, 0.712)
	PPS	ICR	0.711 (0.688, 0.733)	0.727 (0.701, 0.753)	0.687 (0.658, 0.715)
		INV	0.705 (0.680, 0.729)	0.721 (0.693, 0.749)	0.681 (0.650, 0.712)
Model 2: Without OR	PFS	ICR	0.712 (0.697, 0.727)	0.728 (0.708, 0.748)	0.688 (0.664, 0.712)
		INV	0.713 (0.697, 0.727)	0.728 (0.708, 0.748)	0.688 (0.664, 0.712)
	PPS	ICR	0.708 (0.686, 0.728)	0.723 (0.698, 0.748)	0.683 (0.655, 0.711)
		INV	0.695 (0.671, 0.717)	0.710 (0.684, 0.736)	0.670 (0.641, 0.699)
Model 3: Without OR and Treatment	PFS	ICR	0.713 (0.697, 0.728)	-	-
		INV	0.713 (0.697, 0.729)	-	-
	PPS	ICR	0.707 (0.686, 0.729)	-	-
		INV	0.694 (0.672, 0.717)	-	-

Abbreviations: CI, confidence interval; ICR, Independent Central Review; INV, Investigator; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; OR, overall response; PFS, progression-free survival; PPS: post-progression survival; VRd: bortezomib, lenalidomide, and dexamethasone.

In the base case, the model uses progression-free health utilities from Model 2 with PFS investigator assessment, without OR and with a treatment effect due to the statistically significant improvement in utility with IsaVRd versus VRd.

In the IMROZ clinical trial, the EQ-5D questionnaire was administered to patients during assessments at each visit, at the end of treatment and at 90 days post-treatment. According to investigator assessment, a total of 406 patients were included, providing 14,728 utility records before progression and 97 patients post-progression for a total of 272 record. Furthermore, post-progression records were clustered just after the progression event, limiting the ability of the utility model to predict post-progression utility beyond the time of data collection and providing an overly optimistic understanding of the progression health state. According to investigator assessment, 79.8% (217/272) of post-progression records were collected within 6 months of the progression event. Given the limited number of records and the lack of representation of later times post-progression in IMROZ, it is more plausible to use utilities reported in literature searches to inform

the post-progression utility value as the base case in the cost-effectiveness model. In the base-case, post-progression utility was sourced from TA587 as described in Section B.3.10.

Regarding comparators not included in IMROZ trial, IsaVRd utility for PFS was applied to DRd (anti-CD38). Other comparators were applied the VRd PFS utility. The final utility values used in the base-case are presented in Table 64.

Additionally, the IMROZ utility value for the PP health state and Models 1 and 3 were tested in scenario analyses.

Table 64: Utility values used in the base-case analysis

	IsaVRd	DRd	Rd	VMP	VCd	Source
PFS	0.728	0.728	0.688	0.688	0.688	IMROZ
PPS	0.557	0.557	0.557	0.557	0.557	TA587

Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; PFS, progression-free survival; PPS, post-progression survival; Rd, lenalidomide and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone; VRd, bortezomib, lenalidomide, and dexamethasone.

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

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

An SLR was conducted (finalised in January 2023) to identify the economic burden in patients with NDMM. This report was updated on 29 April 2024.

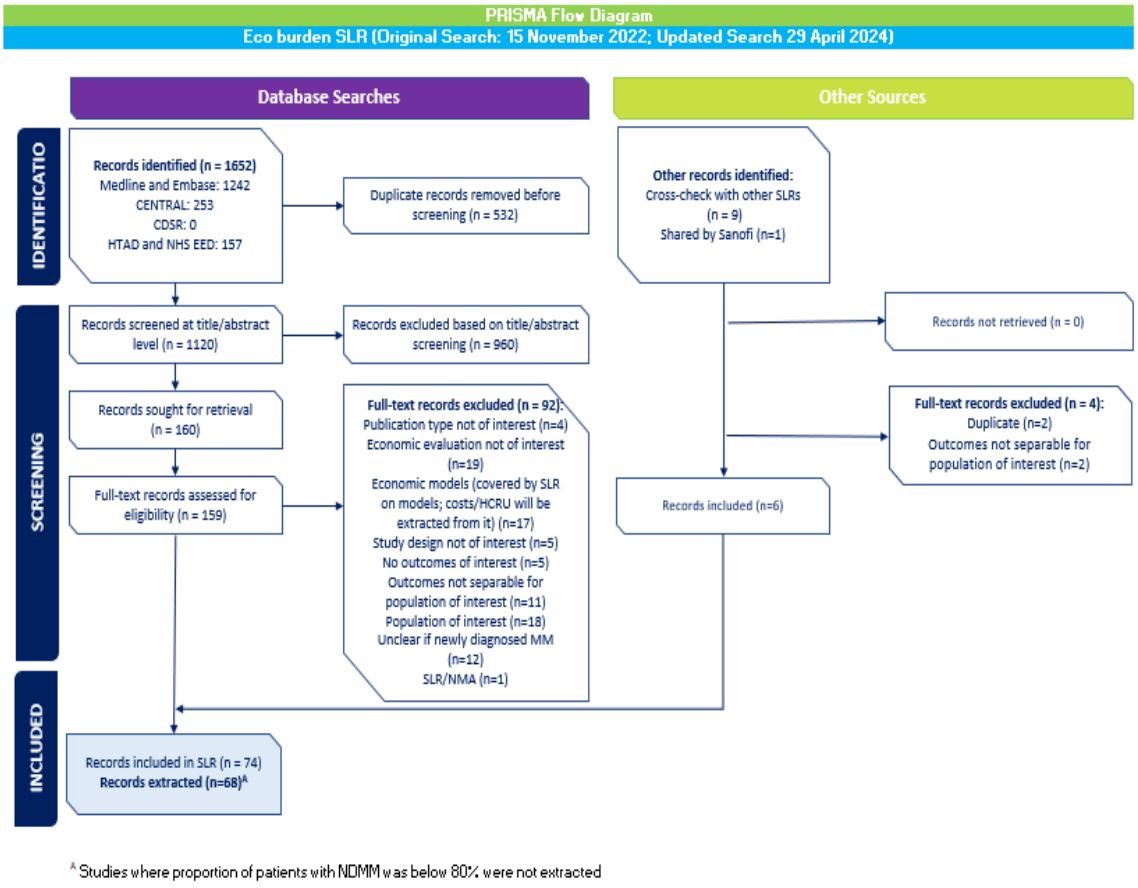
Electronic databases were searched on 15 November 2022 and updated on 29 April 2024 via the OvidSP platform to identify peer-reviewed studies of interest. The databases searched included:

- Embase
- MEDLINE and MEDLINE In-Process
- EconLit
- CENTRAL
- Cochrane Database of Systematic reviews
- HTA Database
- National Health Service Economic Evaluation Database

Additional searches were conducted in conference proceedings, HTA websites and databases, and bibliographies of relevant SLRs published since 2016 to identify any publication not identified in the electronic database search phase.

The PRISMA flow diagram for the updated search (April 2024) is presented in Figure 54. No studies specific to a transplant-ineligible population in England were identified in the SLR. Full details of the searches and results for economic burden studies identified are reported in Appendix I.2.

Figure 54: PRISMA diagram on economic burden (April 2024)



Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; HCRU, healthcare resource utilisation; HTAD, Health Technology Assessment Database; NHS EED, National Health Service Economic Evaluation Database; NMA, network meta-analyses; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; SLR, systematic literature review.
Source: Economic and Humanistic SLR update (106).

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

The list prices of drugs for all modelled interventions are presented in Section B.3.5.4, including subsequent treatments. Drug costs for brand-name treatments were sourced from the Monthly Index of Medical Specialities (MIMS). For conventional treatments that are available as generics, unit costs were sourced from the electronic market information tool (eMIT) or the British National Formulary (BNF). No confidential drug price discounts are applied. All costs were based on 2023/24 releases; therefore, inflation of drug costs was not required.

B.3.5.2.1 Drug acquisition costs

The cost of acquisition per administration was applied in line with the respective dosing schedule, as detailed in Appendix I.7.

The model accounts for relative dosing intensity (RDI), defined as the ratio of the actual dose intensity to the planned dose intensity. Patients who are receiving treatment may not necessarily receive the full course of therapy due to dose reductions. The model applies RDI to drug acquisition costs in the base case, as advised during the system engagement meeting with NICE. For IsaVRd, RDI was derived from the IMROZ clinical study report results. The RDI was sourced from the MAIA trial for DRd and Rd (77), and from the ALCYONE trial for VMP (142). It was

assumed that when daratumumab is administered subcutaneously at a fixed dosage, the RDI is 100%. This is in line with the assumption in TA917 (72). For VCd, due to lack of published data, RDI was assumed to be equal to VMP to maintain a consistent approach across all comparators. RDI is user-amendable for each component of each treatment and varied in sensitivity analyses.

Daratumumab cost can be weighted by the proportion of patients receiving daratumumab intravenously or subcutaneously. In the base case, following clinical guidance and in line with TA917, this is set to 0% of patients receiving IV and 100% receiving SC administration.

For weight- or BSA-based drugs, the 'method of moments' has been applied to estimate the average dose accounting for wastage (no vial sharing). Method of moments is a technique that allows estimation of the average number of vials required per treatment administration when dosing is based on weight or BSA. This method accounts for the distribution of a patient population's weight or BSA, as opposed to a point estimate. The variations in weight and BSA were obtained from the IMROZ trial ITT population. The cost of drugs for which method of moments was used are summarised in Table 65.

Table 65: Drugs that required method of moments adjustments

Treatment	Dose	Adjusted acquisition cost per administration
Isatuximab (Isa)	10 mg/kg	£3,977.84
Bortezomib (V)	1.3 mg/m^2	£67.21
Melphalan (M)	9.0 mg/m^2	£152.82
Prednisone (P)	60.0 mg/m^2	£0.24

Abbreviations: Isa, isatuximab; IV, intravenous; M, melphalan; P, prednisone; V, bortezomib.

It was assumed that no vial sharing occurs between patients for all weight- and BSA-based treatments in the base case. It was assumed that there is no wastage for drugs administered orally.

For lenalidomide where the prescribed dose is determined by patient's renal function, the model weights the cost per administration for the 25 mg and 10 mg doses by the proportion of patients with regular renal function and moderately impaired renal function, respectively (Table 44, Section 3.2.1).

It is also assumed that dexamethasone dosing for patients aged <75 years receiving IsaVRd is applied throughout the model time horizon and does not reduce when patients reach 75 years of age. This is a conservative assumption and may result in a slight over-estimation of IsaVRd drug costs but is assumed to have minimal impact due to the low cost of dexamethasone.

The induction phase dosing schedules and costing were modelled precisely by week. For single regimens and continuous phase dosing, an average frequency of administrations per cycle was calculated and applied to the drug costs to obtain the average cost per cycle.

The discount size and duration are user-amendable for flexibility. Discounts can be applied to all treatments except concomitant treatments.

B.3.5.2.2 Drug administration costs

In addition to the drug acquisition costs, the cost of administration was also considered within the cost-effectiveness model. Administration costs (Table 66) were sourced from NHS reference costs 2022/23, which are the most recent available NHS reference costs.

Administration costs were applied dependent on whether the drug is administered intravenously as a first or subsequent IV dose, SC injection, or oral first or subsequent dose, as per the summary of product characteristics (SmPCs) for each regimen. For IV drugs, it was assumed that patients would receive treatment in a hospital setting at each administration. First and subsequent SC injections are assumed to have the same cost. Subsequent dose oral administration was assumed to be associated with no cost. As per feedback from an NHS pharmacist obtained during the initial appraisal of IsaPd, for combination regimens, only the highest administration cost of any component in the combination was applied at the time of administration. This is in line with the most recent appraisal of IsaPd (TA658) (115).

Table 66: Administration types and associated costs

Administration type	Cost per administration, £	Source
IV - First dose	486.10	NHS reference costs 2022–23. Total HRG: SB13Z – Deliver more complex parenteral chemotherapy at first attendance
IV - Prolonged first dose	544.86	SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance
IV - Subsequent dose	393.16	NHS reference costs 2022–23. Total HRG: SB15Z – Deliver subsequent elements of a chemotherapy cycle
SC - First and subsequent doses	411.99	NHS reference costs 2023-23. Total HRG: SB12Z – Deliver simple parenteral chemotherapy at first attendance
Oral - First dose	322.00	NHS reference costs 2022-23. Total HRG: SB11Z – Deliver exclusively oral chemotherapy
Oral - Subsequent dose	0.00	Assumption

Abbreviations: HRG, healthcare resource group; IV, intravenous; NHS, National Health Service.

B.3.5.2.3 Drug costs summary

The estimated acquisition costs per administration and the cost per dosing regimens are presented in Appendix I.3). The intervention and comparators were modelled to be received according to the TTD curve (Figure 13 in Section B.2.6.1.5).

B.3.5.3 *Adverse reaction unit costs and resource use*

In the base case analysis, the cost of managing Grade 3/4 drug-related AEs that occurred in at least 5% of patients in in each treatment arm of the associated clinical trials were included. Grade 1 and 2 events were not included as they were unlikely to have a notable impact on patient HRQL or costs. The impact on incremental costs of less severe AEs and AEs occurring in fewer than 5% of patients on cost-effectiveness results is likely to be negligible.

The model applies AE costs as a one-off lump-sum when patients enter the model. The one-off cost combines the proportion of patients experiencing the AE with the unit cost.

AE unit costs are presented in Table 67. AE costs have been informed by NHS reference costs 2022/23 (143) and are aligned with the DRd NICE submission (72).

Table 67: Adverse event costs

Adverse event	Cost (£)	Source
Acute Kidney injury	£2,699.75	NHS reference costs 2022/23: Weighted average of LA07H–LA07P: Acute Kidney Injury with Interventions (CC Score 0–11+) and without Interventions (CC Score 0–12+), NEL and NES. Aligns with TA917.
Anaemia	£1,471.23	NHS reference costs 2022/23: Weighted average of SA04G–SA04L: Iron Deficiency Anaemia with CC Score 0–14+, NEL and NES. Aligns with TA917.
Asthenia	£3,149.92	NHS reference costs 2022/23: Weighted average of SA03G–SA03H: Haemolytic Anaemia (CC Score 0–3+), NEL and NES. Aligns with TA917.
Cataract	£1,489.66	NHS reference costs 2022/23: Weighted average of: BZ24D-G: Non-Surgical Ophthalmology with Interventions and without Interventions (CC Score 0–5) NEL and NES. Aligns with TA917.
Chronic kidney disease	£3,609.37	NHS reference costs 2022/23: Weighted average of: LA08G–LA08P Chronic Kidney Disease with Interventions (CC Score 0–6+) and without Interventions (CC Score 0–11+), NEL and NES. Aligns with TA917.
Covid-19 pneumonia	£2,907.31	NHS reference costs 2022/23: Weighted average of DX11A: COVID-19 Infection, with Pneumonia, 19 years and over, NEL and NES
Diarrhoea	£1,882.79	NHS reference costs 2022/23: Weighted average of FD01A–FD01J: Gastrointestinal Infections with Multiple Interventions (CC Score 0–5+), and without Interventions (CC Score 0–8+), NEL and NES. Aligns with TA917.
Fatigue	£1,863.53	NHS reference costs 2022/23: Weighted average of WH17A – C: Admission Related to Social Factors with Interventions (CC Score 0–1+), NEL and NES. Aligns with TA917.
Hyperglycaemia	£1,828.02	NHS reference costs 2022/23: Weighted average of of KB01C–KB01F and KB02G–KB02K: Diabetes with Hypoglycaemic Disorders (CC Score 0–8+) and with Hyperglycaemic Disorders (CC Score 0–8+), NEL and NES. Aligns with TA917.
Hypertension	£1,921.06	NHS reference costs 2022/23: Weighted average of SA08G–SA08J: Other haematological or splenic disorders, with CC score 0–6+, NEL and NES. Aligns with TA917
Hypokalaemia	£1,965.21	NHS reference costs 2022/23: Weighted average of: KC05G, KC05H, KC05J, KC05K, KC05L, KC05M, KC05N: Fluid or Electrolyte Disorders, without Interventions, with CC Score 0-10+, NEL and NES. Aligns with TA917.
Leukopenia	£1,921.06	NHS reference costs 2022/23: Weighted average of SA08G–SA08J: Other haematological or splenic disorders, with CC score 0–6+, NEL and NES. Aligns with TA917
Lymphopenia	£1,921.06	NHS reference costs 2022/23: Weighted average of SA08G–SA08J: Other haematological or splenic disorders, with CC score 0–6+, NEL and NES. Aligns with TA917

Adverse event	Cost (£)	Source
Neutropenia	£1,921.06	NHS reference costs 2022/23: Weighted average of SA08G–SA08J: Other haematological or splenic disorders, with CC score 0–6+, NEL and NES. Aligns with TA917
Peripheral sensory neuropathy	£2,131.39	NHS reference costs 2022/23: Weighted average of AA26C–AA26H: Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury (CC Score 0–15+), NEL and NES.
Pneumonia	£2,662.59	NHS reference costs 2022/23: Weighted average DZ11K-DZ11V: Lobar, Atypical or Viral Pneumonia, with Multiple/Single/No Interventions, with CC Score 0-14+, NEL and NES. Aligns with TA917
Pulmonary embolism	£2,078.03	NHS reference costs 2022/23: Weighted average of DZ09J–DZ09Q: Pulmonary Embolus with Interventions (CC Score 9+) and without interventions (CC Score 0–12NEL and NES. Aligns with TA917.
Syncope	£1,516.43	NHS reference costs 2022/23: Weighted average of EB08A–EB08E: Syncope or collapse (CC Score 0–13+), NEL and NES
Thrombocytopenia	£2,384.62	NHS reference costs 2022/23: Weighted average of SA12G–SA12K: Thrombocytopenia with CC score 0–8+, NEL and NES. Aligns with TA917.

Abbreviations: NEL, non-elective long stay; NES, non-elective short stay; NHS, National Health Service; TA, technology appraisal.

B.3.5.4 *Miscellaneous unit costs and resource use*

B.3.5.4.1 Concomitant treatment costs

The cost of concomitant treatment is included in the model. Concomitant treatments for each comparator were based on associated summaries of product characteristics. Concomitant medications were defined as any drugs given in parallel with the active treatment regimens, excluding any drugs prescribed to manage AEs.

Before isatuximab administration, patients should receive diphenhydramine 25 to 50 mg intravenously (or equivalent), ranitidine 50 mg intravenously (or equivalent) and acetaminophen (paracetamol) 650 to 1,000 mg orally. Once the premedication regimen is completed, isatuximab infusion must start immediately. The model conservatively assumed the highest dose of each premedication is required. It was assumed that daratumumab concomitant treatments, prior to and post-daratumumab administration, are applied simultaneously. The list prices of concomitant treatments are presented in Table 68.

Table 68. Concomitant treatment list prices

Treatment	Pack size	Form	Quantity per unit (mg)	Cost per pack (£)	Source (pack cost)
Paracetamol	24	Tablets	500	1.25	eMIT 2023 - DDG485
Paracetamol	60	Tablets	500	2.71	eMIT 2023 - DDM004
H2 blocker (Cimetidine)	60	Tablets	400	3.61	eMIT 2023 – DAE002

Diphenhydramine	1	150.0 ml oral solution (10mg/5ml)	300	26	MIMS 2023 (Diphenhydramine hydrochlor - Histergan)
Methylprednisolone	1	powder and solvent for solution for injection vials	1000	12.23	eMIT 2023 - DFN009
Aciclovir	25	Tablets	200	0.74	eMIT 2023 - DER023

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; IV, intravenous; MIMS, Monthly Index of Medical Specialties; OBD, on-board device; SC, subcutaneous.

The frequency and cost per administration of concomitant treatments are presented in Table 69.

Table 69: Concomitant treatment cost per administration

Treatment requiring concomitant medication	Dosing schedule	Component	Prescribed dose	Cost per admin (£)	Source
Isatuximab (IMROZ trial protocol (123))	Prior to isatuximab infusion	Paracetamol	1000 mg	£0.09	eMIT 2023 - DDM004
		Diphenhydramine	50 mg	£4.33	MIMS 2023
		H2 blocker (Cimetidine)	50 mg	£3.61	eMIT 2023 – DAE002
Daratumumab (Darzalex SmPC (126))	Prior to daratumumab infusion /injection	Paracetamol	1000 mg	£0.09	eMIT 2023 - DDM004
		Diphenhydramine	50 mg	£4.33	MIMS 2023
	Post daratumumab infusion /injection	Methylprednisolone	20 mg	£0.24	eMIT 2023 - DFN009
Bortezomib (Velcade SmPC (127))	Daily	Aciclovir	200 mg	£0.01	eMIT 2023 – DER023

Abbreviations: eMIT, electronic market information tool; mg, milligram; MIMS, Monthly Index of Medical Specialities; SmPC, Summary of Product Characteristics.

B.3.5.4.2 Monitoring costs

Monitoring costs were dependent on whether patients are on-/off-treatment. On-treatment costs were applied to on-treatments patients in the PFS state and to all patients in the PPS state to account for the fact that patients are treated with subsequent treatments until death in the PPS state. Off-treatment costs were applied to off-treatment patients in the PFS state after discontinuing the first-line treatment. Medical resources included haematologist visits and monitoring tests such as full blood count. The complete list of medical resources and unit costs is presented in Table 70.

The model allows a micro-costing approach to be undertaken whereby the frequencies of individual resources are broken down depending on treatment status (Table 71). Medical resource use

frequency was identical across treatment arms aligned with previous HTA submissions (TA917 (72), TA573 (replaced by TA897) (110), TA763 (112)).

All monitoring costs were derived from the latest NHS reference costs 2022/23 (Table 70) (143). The medical resources and frequencies are aligned with previous HTA submissions (TA917 (72), TA573 (replaced by TA897) (110), TA763 (112)).

Table 70: Resource use unit costs

Resource	Cost (£)	Source
Haematologist visit	£190.77	NHS Reference Cost 2022-2023, WF01A (303), weighted average of CL, NCL, in Outpatient care (143)
Full blood count	£3.00	NHS Reference Cost 2022-2023, DAPS05: Hematology (143)
Biochemistry	£2.00	NHS Reference Cost 2022-2023, DAPS04: clinical biochemistry (143)
Protein electrophoresis	£9.00	NHS Reference Cost 2022-2023, DAPS06 - immunology service (143)
Immunoglobin	£9.00	NHS Reference Cost 2022-2023, DAPS06 - immunology service (143)
Urinary light chain excretion	£9.00	NHS Reference Cost 2022-2023, DAPS06 - immunology service (143)

Abbreviations: CL, consultant led; NCL, non-consultant led; NHS, National Health Service: OP, outpatient.

Table 71: Medical resources for monitoring patients based on on/off treatment

Item	On-treatment		Off-treatment		Source
	Frequency per 28 days	Frequency per cycle	Frequency per 28 days	Frequency per cycle	
Haematologist visit	0.92	0.23	0.32	0.08	Assumed to be equal to that reported in TA917, and equal across all regimens.
Full blood count	0.84	0.21	2.56	0.64	
Biochemistry	0.76	0.19	1.32	0.33	
Protein electrophoresis	0.52	0.13	0.72	0.18	
Immunoglobin	0.48	0.12	0.76	0.19	
Urinary light chain excretion	0.2	0.05	0.2	0.05	
Total cost	**£190.35**	**£95.18**	**£86.49**	**£43.24**	Calculation

Abbreviation: TA, technology appraisal.

B.3.5.4.3 Subsequent treatment costs

Subsequent treatments were assumed to only affect costs, with no direct effect on efficacy as its impact was assumed to be implicitly included in the modelled OS estimates. Expert opinion informed the distribution of subsequent treatments at each line of therapy. This is because granular information on regimens is not available for comparators, current follow-up in clinical trials does not include complete data for later lines of therapy, and a consistent approach was necessary for all

regimens. This also follows precedence from the NICE appraisal of DRd (TA917) (33). Additional detail is provided in Appendix I.4.

Subsequent treatment distribution

The model included the cost of subsequent treatments in the second, third, and fourth lines. This aligns with IMROZ data, where a proportion of patients received regimens at the fourth line. This aligns with a real-world study by Yong et al. in which 15% and only 1% of patients reached the fourth and fifth line respectively in MM treatment across Belgium, France, Germany, Italy, Spain, Switzerland, and the UK (144).

The distribution of patients across the lines of treatment was obtained from an advisory board meeting with 10 clinicians from England and Wales to accurately reflect treatments received in current NHS clinical practice. The mean subsequent treatment distributions by line are presented in Table 76. The distribution of subsequent treatment for patients per individual clinician from England and Wales who participated in the UK advisory board is provided in Appendix I.4. The clinicians indicated patients who received frontline IsaVRd and progressed on it would not receive an anti-CD38 or lenalidomide as a second-line treatment. Bortezomib is administered solely during the induction phase, making it unlikely that patients will become refractory to it. As a result, patients in the IsaVRd and DRd arms are expected to have very similar, if not identical, subsequent treatments.

Attrition rates between lines of treatment were applied to exclude patients who do not receive treatment at any line. These rates were derived from pivotal trials of each first-line treatment between 1L and 2L (Table 72) (76-79, 103, 145). For transitions between 2L and 3L, and between 3L and 4L, data from clinical trials were unavailable, so attrition rates were sourced from Yong et al., with the same proportions applied irrespective of previous lines of treatment (144). Since the proportion of patients at 3L and 4L depends on the proportion at 2L, which varies by comparator, these proportions were converted into rates relative to the previous line (Table 73 and Table 74). The final proportions of patients without treatment at each line were then recalculated and are described in Table 75. The final distribution of subsequent therapies, based on clinicians' estimates and attrition rates, is provided in Table 77.

The rationale for modelling different attrition rates between 1L and 2L by first-line treatment is based on the observation that longer PFS correlates with a lower proportion of patients receiving subsequent treatment after a PFS event. In the context of IsaVRd, this can be explained by a higher proportion of deaths within the PFS state whilst obtaining better PFS and OS.

In the IMROZ trial, patients are 71.63 years old, and given the long PFS observed for IsaVRd, more patients are expected to die due to age and comorbidities. For example, at the point of progression, mean age of a patients with a PFS event is for IsaVRd is 81.2 years old. Therefore, less patients are likely to receive subsequent therapies.

Consequently, the proportion of patients without treatment at the second line is higher for IsaVRd compared with comparators (Table 73 and Table 74). These assumptions have been confirmed by clinicians based on observations in clinical practice. Clinical trial data were not available for VCd, so the proportion of patients without treatment at each line estimated for VMP was used for consistency between comparators.

Furthermore, patients treated with IsaVRd and DRd are eligible for the same types and distributions of subsequent treatments. However, based on the maximum follow-up available in the IMROZ trial, the restricted mean survival time (RMST) of progression-free survival at the second

line (PFS2 − PFS) is 2.20 months for IsaVRd and 4.72 months for DRd. This indicates a 115% shorter time spent/lower proportion of patients at the second line of treatment with IsaVRd compared with DRd (Figure 55).

Table 72: Proportion of patients with a subsequent treatment among patients with a PFS event by treatment at 1L – highlighted in bold

	IsaVRd	DRd	Rd	VMP	VCd
PFS ICR, % (n)	100 (84)	100 (160)	100 (217)	100 (265)	100 (265)
Progressive disease, % (n)	60 (50)	70 (112)	79 (171)	87 (230)	87 (230)
Progressive disease with subsequent treatment, % (n)	**43 (36)**	**57 (91)**	**67 (145)**	**67 (177)**	**67 (177)**
Death, % (n)	40 (34)	30 (48)	21 (46)	13 (35)	13 (35)
Source	IMROZ (76)	MAIA (77-79)	MAIA (77-79)	ALCYONE (103, 145)	Assumed equal to VMP

Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; ICR, Independent Central Review; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

Table 73: Attrition rates described in Yong et al.

	Proportion with a treatment at each LoT (%)	Proportion with a treatment at each LoT, re-based to 100% (%)	Proportion without treatment at each LoT (%)	Proportion without treatment at each LoT, relative to the previous line (%)
1L	95%	100%	0%	0%
2L	61%	64%	36%	36%
3L	38%	40%	60%	38%
4L	15%	16%	84%	61%

Abbreviations: L, line; Lot, line of therapy.
Source: Yong et al, (144).

Table 74: Proportion of patients without treatment estimated from clinical trials and Yong et al., relative to the previous line of treatment

	IsaVRd	DRd	Rd	VMP	VCd	Source
1L	0%	0%	0%	0%	0%	Assumption
2L	57%	43%	33%	33%	33%	Clinical trials (highlighted in bod in Table 72)
3L	38%	38%	38%	38%	38%	Yong et al. (144)
4L	61%	61%	61%	61%	61%	Yong et al. (144)

Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; L, line; Rd, lenalidomide and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

Table 75: Final proportion of patients without treatment applied in the cost-effectiveness model, relative to the first line of treatment

	IsaVRd	DRd	Rd	VMP	VCd	Source
1L	0%	0%	0%	0%	0%	Calculation
2L	57%	43%	33%	33%	33%	
3L	73%	65%	58%	58%	58%	
4L	89%	86%	84%	84%	84%	

Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; L, line; Rd, lenalidomide and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

Table 76: Subsequent treatment distribution according to UK advisory board

2L treatment							
To / From	**Kd**	**Rd**	**Vd**	**KRd**	**DVd**	**VCd**	-
IsaVRd	35.5%	0.1%	19.3%	0.0%	0.1%	45.0%	-
VMP	7.0%	22.0%	0.0%	14.0%	57.0%	0.0%	-
DRd	32.5%	0.2%	18.1%	0.2%	0.0%	49.0%	-
VCd	7.2%	27.2%	1.1%	15.0%	48.3%	1.1%	-
Rd	13.5%	0.0%	7.5%	0.0%	70.5%	8.5%	-
3L treatment							
To / From	**Rd**	**Pd**	**IxaRd**	**PanVd**	**Vd**	**VCd**	**CTd**
IsaVRd	0.0%	17.0%	0.0%	13.0%	10.5%	10.0%	49.5%
VMP	24.0%	0.0%	62.0%	2.0%	0.0%	0.0%	12.0%
DRd	0.0%	16.0%	0.0%	22.0%	11.5%	12.0%	38.5%
VCd	20.6%	0.0%	45.0%	3.9%	2.8%	0.6%	27.2%
Rd	0.0%	16.0%	0.0%	23.0%	8.5%	12.0%	40.5%
4L treatment							
To / From	**Pd**	**IxaRd**	**Dara**	**PanVd**	-	-	-
IsaVRd	80.0%	0.0%	0.0%	20.0%	-	-	-
VMP	94.0%	0.0%	0.0%	6.0%	-	-	-
DRd	80.0%	0.0%	0.0%	20.0%	-	-	-
VCd	78.9%	2.2%	7.8%	11.1%	-	-	-
Rd	71.0%	0.0%	9.0%	20.0%	-	-	-

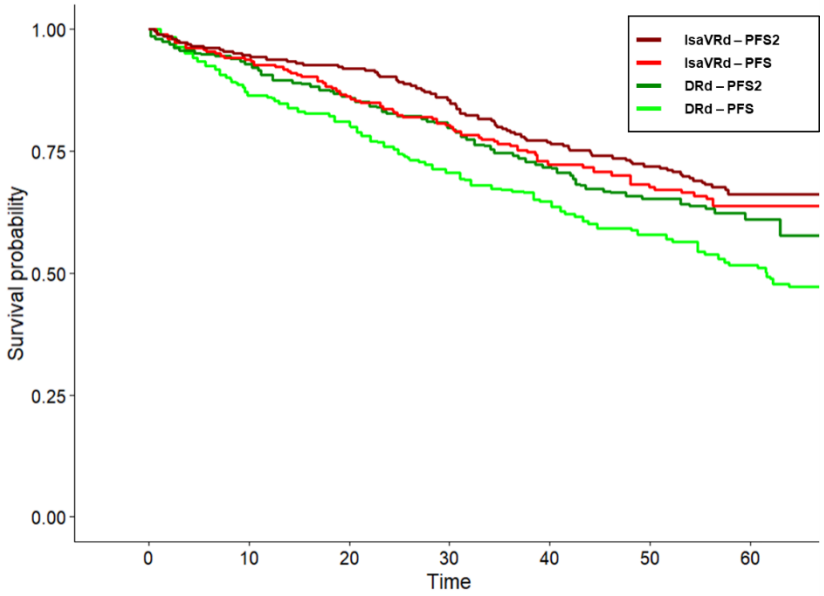
Abbreviations: 2L, second-line; 3L, third-line; 4L, fourth-line; CTd, cyclophosphamide, thalidomide, and dexamethasone; Dara, daratumumab; DRd, daratumumab, lenalidomide, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; IxaRd, ixazomib, lenalidomide, and dexamethasone; Kd, carfilzomib and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; PanVd, panobinostat, bortezomib, and dexamethasone; Pd, pomalidomide and dexamethasone; Rd, lenalidomide and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; Vd, bortezomib and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

Table 77: Subsequent treatment distribution accounting for attrition rates

2L treatment								
To / From	**Kd**	**Rd**	**Vd**	**KRd**	**DVd**	**VCd**	-	**No treatment**
IsaVRd	15.2%	0.0%	8.3%	0.0%	0.0%	19.3%	-	57.1%
VMP	4.7%	14.7%	0.0%	9.4%	38.1%	0.0%	-	33.2%
DRd	18.5%	0.1%	10.3%	0.1%	0.0%	27.9%	-	43.1%
VCd	4.8%	18.2%	0.7%	10.0%	32.3%	0.7%	-	33.2%
Rd	9.0%	0.0%	5.0%	0.0%	47.1%	5.7%	-	33.2%
3L treatment								
To / From	**Rd**	**Pd**	**IxaRd**	**PanVd**	**Vd**	**VCd**	**CTd**	**No treatment**
IsaVRd	0.0%	4.5%	0.0%	3.5%	2.8%	2.7%	13.2%	73.3%
VMP	10.0%	0.0%	25.8%	0.8%	0.0%	0.0%	5.0%	58.4%
DRd	0.0%	5.7%	0.0%	7.8%	4.1%	4.3%	13.6%	64.6%
VCd	8.6%	0.0%	18.7%	1.6%	1.2%	0.2%	11.3%	58.4%
Rd	0.0%	6.7%	0.0%	9.6%	3.5%	5.0%	16.9%	58.4%
4L treatment								
To / From	**Pd**	**IxaRd**	**Dara**	**PanVd**	-	-	-	**No treatment**
IsaVRd	8.4%	0.0%	0.0%	2.1%	-	-	-	89.5%
VMP	15.4%	0.0%	0.0%	1.0%	-	-	-	83.6%
DRd	11.2%	0.0%	0.0%	2.8%	-	-	-	86.0%
VCd	13.0%	0.4%	1.3%	1.8%	-	-	-	83.6%

Abbreviations: 2L, second-line; 3L, third-line; 4L, fourth-line; CTd, cyclophosphamide, thalidomide, and dexamethasone; Dara, daratumumab; DRd, daratumumab, lenalidomide, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; IxaRd, ixazomib, lenalidomide, and dexamethasone; Kd, carfilzomib and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; PanVd, panobinostat, bortezomib, and dexamethasone; Pd, pomalidomide and dexamethasone; Rd, lenalidomide and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; Vd, bortezomib and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

Figure 55: PFS and PFS2 of IsaVRd and DRd from the IMROZ and MAIA clinical trials



Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; PFS, progression-free survival; PFS2; progression-free survival at next line of therapy.

Subsequent treatment duration

The costs of subsequent treatments were calculated for each line and consider acquisition and administration costs separately. These costs were based on the unit costs (Appendix I.7), the reported dosing (Appendix I.3) and treatment duration associated with each regimen, which was estimated using the median TTP/PFS (Table 85 in Appendix I.3). Subsequent treatment durations for the 2L and 3L are sourced from NICE appraisal TA917; 4L is sourced from NICE appraisal TA763 as this was not reported in TA917. Where treatments are not included in TA763, they are assumed equal to pomalidomide and dexamethasone (Pd) as Pd is the minimum effective treatment given to patients in 4L. These costs were then multiplied by the subsequent treatment distribution of the cohort receiving each treatment regimen (Table 77) to generate a lump sum total cost across all treatment lines.

This cost can then be imputed on the time horizon after progression disease or after treatment discontinuation. Spreading the cost over the time horizon may be regarded as advantageous compared with a one-off cost approach as it better captures the effect of annual discounting and deaths on the number of patients on subsequent treatment. The progression-based approach was used in the base case. The discontinuation-based approach was tested in a scenario analysis.

To apply the cost post progression, the overall subsequent treatment cost was divided by the total proportion of patients in the PPS state and then multiplied by the proportion of patients in each cycle in the same PPS health state.

Additionally, the final option for implementing the overall subsequent treatment cost in the model assumes that the total cost over the time horizon depends on the duration spent in progression; thus, the longer the time in the progressed health state, the higher the total cost of subsequent therapies over the time horizon for a given treatment distribution. In this approach, a weekly subsequent therapy cost is applied if patients are in the progressed health state. To calculate this cost, the total subsequent treatment cost for each regimen in subsequent lines is first calculated according to the pivotal trial dosing schedule over the mTTP/PPS of the regimen. This total cost is then divided by the mTTP/PFS to compute an average cost per week for each regimen. The

average weekly cost is weighted by the distribution of subsequent treatments in that line to obtain a weighted cost per week for each line (2L, 3L, and 4L). The cost per week applied to patients in the progressed state is the sum of the weighted costs per week for 2L, 3L, and 4L. As the time spent in the progressed health state varies according to different modelling assumptions, the total costs of subsequent treatment across the time horizon will also vary. This per-cycle approach is tested in scenario analysis.

Subsequent treatment costs summary

Table 78 presents the total lump sum subsequent therapies costs based on the subsequent treatment distributions, drug costs, administration costs and subsequent treatment durations, applied at the point disease progression.

Similarly to 1L drug costs, acquisition and administration costs were not inflated as they used 2023/24 releases of inputs. The list prices of subsequent treatments are provided in Appendix I.7.

The method described below is considered a conservative case for the following reason. The cost of subsequent treatment is based on the weighted duration of each clinical trial at 2L, 3L, and 4L and is shorter than the time spent in the PPS health state for each comparator. As a result, the costs of subsequent therapies are underestimated more for comparators than for IsaVRd, which impact the overall cost-effectiveness analysis.

Table 78: Subsequent therapy costs

Treatment line	IsaVRd	DRd	Rd	VCd	VMP
Acquisition costs (£)					
2L subsequent therapy cost	[redacted]	[redacted]	£97,818.77	£72,670.00	£81,310.59
3L subsequent therapy cost	[redacted]	[redacted]	£12,333.80	£40,143.53	£53,027.57
4L subsequent therapy cost	[redacted]	[redacted]	£7,295.11	£7,344.88	£7,383.58
Total acquisition costs	[redacted]	[redacted]	£117,447.68	£120,158.41	£141,721.74
Administration costs (£)					
2L subsequent therapy cost	[redacted]	[redacted]	£19,817.96	£15,960.49	£17,063.08
3L subsequent therapy cost	[redacted]	[redacted]	£3,212.96	£853.46	£531.71
4L subsequent therapy cost	[redacted]	[redacted]	£592.03	£396.19	£232.88
Total administration costs	[redacted]	[redacted]	£23,622.94	£17,210.14	£17,827.66
Overall costs (£)					
Total	[redacted]	[redacted]	£141,070.62	£137,368.55	£159,549.40

Abbreviations: 2L, second line; 3L, third line; 4L, fourth line; DRd, daratumumab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

B.3.5.4.4 End-of-life costs

A one-off end-of-life cost of £13,314 was applied from the payer perspective to patients at the point of dying to reflect the cost of terminal care. This was taken from Unit Costs of Health and Social Care 2023 for cancer-specific population representing the cost of hospital and social care services per decedent in the final year of life (146).

B.3.6 *Severity*

Based on the QALY shortfall calculator published by Schneider et al. (147), IsaVRd in TI-NDMM does not meet the criteria for the application of a QALY modifier.

B.3.7 *Uncertainty*

Probabilistic and deterministic sensitivity analyses and scenario analyses were conducted to address the uncertainty.

B.3.8 *Managed access proposal*

As this submission details a robust evidence package for IsaVRd and a mature length of follow-up for IMROZ, Sanofi consider IsaVRd suitable for routine commissioning. As per the latest datacut, the IMROZ trial has a median follow-up of 59.73 months and IsaVRd has demonstrated a statistically significant reduction in PFS compared with current NHS best standard of care, DRd, in TI patients with NDMM who are not eligible for ASCT (HR: [redacted]). Further data cuts are expected to confirm the substantial clinical benefit of IsaVRd for this population.

B.3.9 *Summary of base-case analysis inputs and assumptions*

B.3.9.1 *Summary of base-case analysis inputs*

The base case options for the model and the rationale and justifications behind them are presented in Table 79.

Table 79: Summary of variables applied in the economic model

Variable	Value					Confidence interval (distribution)	Reference to section in submission
Model settings							
Discount rate (costs and benefits)	3.5%					-	Section B.3.2.2.2
Time horizon	29 years					-	Section B.3.2.2.1
Patient baseline characteristics							
Mean age	71.63 years					71.23, 72.03	Section B.3.2.1
Mean body weight	73.58 kg					72.14, 75.02	Section B.3.2.1
Mean BSA	1.8 m^2					1.78, 1.82	Section B.3.2.1
Male	53%					0.43, 0.63	Section B.3.2.1
Survival inputs							
	PFS	**OS**	**ToT**				
Extrapolation for IsaVRd	Gamma	Gompertz	Exponential			-	Section B.3.3.2 Section B.3.3.3 Section B.3.3.4
Extrapolation for DRd	Gamma	Gompertz	HR versus IsaVRd TTD			-	Section B.3.3.2 Section B.3.3.3 Section B.3.3.4
Extrapolation for Rd	Gamma	Gompertz	HR versus Rd PFS			-	Section B.3.3.2 Section B.3.3.3 Section B.3.3.4
Extrapolation for VCd	Gamma	Gompertz	HR versus VCd PFS			-	Section B.3.3.2 Section B.3.3.3 Section B.3.3.4
Extrapolation for VMP	Gamma	Gompertz	HR versus VMP PFS			-	Section B.3.3.2 Section B.3.3.3 Section B.3.3.4
AEs							
	IsaVRd	**DRd**	**Rd**	**VCd**	**VMP**		

Neutropenia	79	197	135	136	136		Section B.3.3.5
Lymphopenia	0	60	41	67	67		Section B.3.3.5
Thrombocytopenia	31	32	34	126	126		Section B.3.3.5
Anaemia	0	61	79	62	62		Section B.3.3.5
Pneumonia	53	70	39	22	22		Section B.3.3.5
Hypokalaemia	0	46	36	22	22		Section B.3.3.5
Diarrhoea	20	32	22	25	25		Section B.3.3.5
Fatigue	21	32	17	25	25		Section B.3.3.5
Hypertension	0	31	16	0	0		Section B.3.3.5
Asthenia	7	19	17	21	21		Section B.3.3.5
Acute kidney disease	0	19	12	0	0		Section B.3.3.5
Cataract	41	40	39	0	0		Section B.3.3.5
Utility inputs							
	IsaVRd	**DRd**	**Rd**	**VCd**	**VMP**	-	Section B.3.4.6
PF (SD)	0.728	0.728	0.688	0.688	0.688	-	Section B.3.4.6
PD (SD)	0.557						
Adverse event disutility							
Neutropenia	-0.15					0.12, 0.18	Section B.3.4.5
Lymphopenia	-0.07					0.06, 0.08	Section B.3.4.5
Thrombocytopenia	-0.31					0.25, 0.37	Section B.3.4.5
Leukopenia	-0.07					0.06, 0.08	Section B.3.4.5
Anaemia	-0.31					0.25, 0.37	Section B.3.4.5
Pneumonia	-0.19					0.15, 0.23	Section B.3.4.5
Hypokalaemia	-0.07					0.06, 0.08	Section B.3.4.5
Pulmonary embolism	-0.31					0.25, 0.37	Section B.3.4.5
Hyperglycaemia	-0.15					0.12, 0.18	Section B.3.4.5
Diarrhoea	-0.10					0.08, 0.12	Section B.3.4.5

Fatigue	-0.12					0.10, 0.14	Section B.3.4.5
Hypertension	-0.15					0.12, 0.18	Section B.3.4.5
Asthenia	-0.12					0.10, 0.14	Section B.3.4.5
Acute kidney disease	-0.18					0.15, 0.22	Section B.3.4.5
Chronic kidney disease	-0.05					0.04, 0.06	Section B.3.4.5
Cataract	-0.01					0.01, 0.01	Section B.3.4.5
Resource use							
	On treatment		**Off treatment**			-	
Haematologist visit	0.92		0.32			-	Section B.3.5.4.2
Biochemistry	0.76		1.32			-	Section B.3.5.4.2
Protein electrophoresis	0.52		0.72			-	Section B.3.5.4.2
Immunoglobulin	0.48		0.76			-	Section B.3.5.4.2
Urinary light chain excretion	0.2		0.2			-	Section B.3.5.4.2
Cost inputs							
IsaVRd	£3791.71					-	Section B.3.5.2.1
DRd	£4322.77					-	Section B.3.5.2.1
Rd	£5.46						Section B.3.5.2.1
VCd	£64.23					-	Section B.3.5.2.1
VMP	£65.54					-	Section B.3.5.2.1
Subsequent therapies							
	IsaVRd	**DRd**	**Rd**	**VCd**	**VMP**		
Kd - 2L	15.22%	18.48%	9.02%	4.82%	4.68%	-	Section B.3.5.4.3
Rd - 2L	0.04%	0.11%	0.00%	18.18%	14.69%	-	Section B.3.5.4.3
Vd - 2L	8.27%	10.29%	5.01%	0.74%	0.00%	-	Section B.3.5.4.3
KRd - 2L	0.00%	0.11%	0.00%	10.02%	9.35%	-	Section B.3.5.4.3
DVd - 2L	0.04%	0.00%	47.11%	32.28%	38.07%	-	Section B.3.5.4.3
VCd - 2L	19.29%	27.87%	5.68%	0.74%	0.00%	-	Section B.3.5.4.3

No active treatment - 2L	57.14%	43.13%	33.18%	33.21%	33.21%	-	Section B.3.5.4.3
Rd - 3L	0.00%	0.00%	0.00%	8.55%	9.99%	-	Section B.3.5.4.3
Pd - 3L	4.54%	5.67%	6.66%	0.00%	0.00%	-	Section B.3.5.4.3
IxaRd - 3L	0.00%	0.00%	0.00%	18.73%	25.80%	-	Section B.3.5.4.3
PanVd - 3L	3.47%	7.80%	9.57%	1.62%	0.83%	-	Section B.3.5.4.3
Vd - 3L	2.80%	4.07%	3.54%	1.16%	0.00%	-	Section B.3.5.4.3
VCd - 3L	2.67%	4.25%	5.00%	0.23%	0.00%	-	Section B.3.5.4.3
CTd - 3L	13.22%	13.64%	16.86%	11.33%	4.99%	-	Section B.3.5.4.3
No active treatment – 3L	73.30%	64.57%	58.37%	58.39%	58.39%	-	Section B.3.5.4.3
Rd - 4L	0.00%	0.00%	0.00%	0.00%	0.00%	-	Section B.3.5.4.3
Pd - 4L	8.43%	11.19%	11.67%	12.96%	15.44%	-	Section B.3.5.4.3
IxaRd- 4L	0.00%	0.00%	0.00%	0.36%	0.00%	-	Section B.3.5.4.3
Dara monotherapy - 4L	0.00%	0.00%	1.48%	1.28%	0.00%	-	Section B.3.5.4.3
IsaPd - 4L	0.00%	0.00%	0.00%	0.00%	0.00%	-	Section B.3.5.4.3
PanVd - 4L	2.11%	2.80%	3.29%	1.82%	0.99%	-	Section B.3.5.4.3
No active treatment - 4L	89.46%	86.01%	83.57%	83.58%	83.58%	-	Section B.3.5.4.3
Concomitant medication costs							
Paracetamol	£1.25					1.02, 1.51	Section B.3.5.4.1
Paracetamol	£2.71					2.20, 3.27	Section B.3.5.4.1
H2 blocker (Cimetidine)	£3.61						Section B.3.5.4.1
Diphenhydramine	£26					21.15, 31.34	Section B.3.5.4.1
Methylprednisolone	£12.23					9.95, 14.74	Section B.3.5.4.1
Aciclovir	£0.74					0.60, 0.89	Section B.3.5.4.1
Administration costs							
IV - First dose	£486.10					395.51, 585.90	Section B.3.5.2.2
IV - Prolonged first dose	£544.86					443.32, 656.71	Section B.3.5.2.2
IV - Subsequent dose	£393.16					319.89, 473.88	Section B.3.5.2.2

Injection - First/Subsequent dose	£411.99	335.21, 496.57	Section B.3.5.2.2
Oral - First dose	£322.00	261.99, 388.10	Section B.3.5.2.2
Oral - No cost	£0.00	0.00, 0.00	Section B.3.5.2.2
Monitoring costs			
Haematologist visit	£190.77	155.22, 229.94	Section B.3.5.4.2
Full blood count	£3.00	2.44, 3.62	Section B.3.5.4.2
Biochemistry	£2.00	1.63, 2.41	Section B.3.5.4.2
Protein electrophoresis	£9.00	7.32, 10.85	Section B.3.5.4.2
Immunoglobin	£9.00	7.32, 10.85	Section B.3.5.4.2
Urinary light chain excretion	£9.00	7.32, 10.85	Section B.3.5.4.2
AE costs			
Neutropenia	£1,921.06	1563.05, 2315.44	Section B.3.5.3
Anaemia	£1,471.23	1197.05, 1773.26	Section B.3.5.3
Lymphopenia	£1,921.06	1563.05, 2315.44	Section B.3.5.3
Leukopenia	£1,921.06	1563.05, 2315.44	Section B.3.5.3
Thrombocytopenia	£2,384.59	1940.20, 2874.12	Section B.3.5.3
Pneumonia	£2,662.59	2166.39, 3209.20	Section B.3.5.3
Hypokalaemia	£1,965.21	1598.97, 2368.65	Section B.3.5.3
Cataract	£1,489.66	1212.05, 1795.47	Section B.3.5.3
Diarrhoea	£1,882.79	1531.92, 2269.31	Section B.3.5.3
Fatigue	£1,863.53	1516.24, 2246.10	Section B.3.5.3
Hypertension	£1,921.06	1563.05, 2315.44	Section B.3.5.3
Hyperglycaemia	£1,828.02	1487.35, 2203.30	Section B.3.5.3
Pulmonary embolism	£2,078.03	1690.77, 2504.63	Section B.3.5.3
Asthenia	£3,149.92	2562.90, 3796.57	Section B.3.5.3
Acute Kidney injury	£2,699.75	2196.62, 3253.97	Section B.3.5.3
Chronic kidney disease	£3,609.37	2936.73, 4350.33	Section B.3.5.3

Peripheral sensory neuropathy	£2,131.39	1734.19, 2568.95	Section B.3.5.3
Syncope	£1,516.43	1233.83, 1827.74	Section B.3.5.3
Covid-19 pneumonia	£2,907.31	2365.51, 3504.15	Section B.3.5.3

Abbreviations: AE, adverse event; DRd, daratumumab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; OS, overall survival; PFS, progression-free survival; ToT, time to treatment; VCd, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone; VRd, bortezomib, lenalidomide, and dexamethasone

B.3.9.2 *Assumptions*

Table 80 presents the key model assumptions included within the cost-effectiveness model.

Table 80: Modelling assumptions

Parameter	Assumption (base case)	Justification	Addressed in scenario analysis; rationale for scenario analysis

Survival	• Survival for IsaVRd is modelled using IMROZ trial data:
	  ○ OS: Gompertz distribution
	  ○ PFS: Gamma distribution
	  ○ TTD: Exponential distribution
	• OS and PFS for non-IMROZ comparators are modelled using non-proportional MAICs or IPW (time-varying HRs)
	• HR is fixed from the end of the trial follow-up for OS.
	• TTD for DRd is modelled using proportional hazard MAIC (constant HR)
	• TTD for other non-IMROZ comparators is modelled using a HR vs PFS, derived using median duration of treatment and median PFS
	• Life tables: All patients are assumed "dead" at 100 years of age. Mortality rate = 1
		• IMROZ is the primary clinical trial providing evidence for IsaVRd and the comparison versus VRd
		• Unanchored MAIC was required to estimate relative effects between IsaVRd and DRd, VMP, CTd, VTd and Rd, due to the lack of a connected network of evidence.
		• Non-proportional MAIC data was used due to evidence of non-proportional hazards in several MAICs, including all daratumumab-based regimens, , except for TTD versus DRd
		• All patients dying by age 100 is standard practice in cost-effectiveness modelling and aligns with NICE guidance
			The following scenarios were conducted:
			• Scenario 9.a Tests base case without fixing the HR
			• Scenario 9. b Compares OS using Gen-gamma distribution
			• Scenario 10.a Fixing HR for PFS
			• Scenario 10.b PFS: Gompertz
			• Scenario 10.c PFS: Weibull
			• Scenario 11.a TTD: Gamma distribution
			• Scenario 11.b TTD: Weibull distribution
			• Scenario 11.c TTD DRd: HR between MAIA PFS and TTD
			• Scenario 11.d TTD = PFS
			• Scenario 11.e TTD: naïve TTD for DRd
			• Scenario 11.f TTD HR IsaVRd vs DRd = 1
			• Scenario 12.a - constant HR MAIC as an alternative to the base case
			• Scenario 12.b standard NMA as an alternative to the base case.

Costs	• Relevant costs include direct 1L and subsequent therapies drug acquisition, administration, AE, monitoring and end-of-life care • When multiple unit sizes are available for a drug, the size with the cheapest per-unit cost was collected and used in the analysis • Drug wastage: wastage is assumed. • RDIs included where available • All costs are stated in Great Britain Pound (GBP) • Drug acquisition and administration costs and concomitant drugs are applied during TTD	• Full justification for costing choices are presented in section B.3.5. Choices align with NICE guidance or precedents set in previous NICE appraisals such as TA917	The following scenarios were conducted: • Scenario 3 excludes wastage. • Scenario 4 applies admin costs for all treatment components of combination treatments • Scenario 5a assumes RDI is 100% • Scenario 5b applies RDI to both administration and acquisition costs • Scenario 6 assesses the impact of 1% for Dara IV • Scenario 7a-7j -assess individual clinician estimates for subsequent therapies

Parameter	Assumption (base case)	Justification	Addressed in scenario analysis; rationale for scenario analysis
	• AE costs are applied as a one-time cost • Subsequent treatment cost is as a lump-sum cost as long as patients are in the progressed health state, • Monitoring costs are applied differently when patients are on/off treatment • End-of-life cost is applied when patients die.		• Scenario 8a applies same attrition rate to all comparators • Scenario 8b assess subsequent treatment costs applied after 1L discontinuation and not progression disease • 8c assess a cost per cycle approach to subsequent therapy costing to account for the time spent in the PPS state
Utilities	• The base case utilities are derived from EQ-5D-3L utilities regressions using inputs from the IMROZ analyses for progression-free health state and from the literature for post- progression health state. • AE disutility is applied as a one-off utility decrement • Age-related general population utility multiplier is applied	• Utilises available trial data for the progression-free health state. EQ-5D-3L is used in alignment with the NHS and PPS perspective and NICE reference case • Utilises available data from the literature to better represent the health state utility in post-progression health state	The following scenarios were conducted: • Scenario 13.a Utilities: PFS model 1 with OR • Scenario 13.b Utilities: PFS no treatment effect • Scenario 13.c Utilities: PPS IMROZ • Scenario 13. d Utilities: PPS Hatswell

Abbreviations: AE, adverse event; DRd, daratumumab, lenalidomide, and dexamethasone; EQ-5D-3L, European quality of life survey – 5 dimensions - 3 levels; HR, hazard ratio; IPW, inverse probability weighting; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; Rd, lenalidomide and dexamethasone; RDI, relative dose intensity; TA, technology appraisal; TTD, time to treatment discontinuation; VCd, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone; VRd, bortezomib, lenalidomide, and dexamethasone

B.3.10 *Base-case results*

B.3.10.1 *Base-case incremental cost-effectiveness analysis results*

Base case results and the net health benefit for pairwise comparison are presented in Table 81 and Table 82 using the list prices and PAS price for isatuximab only, respectively.

The full incremental cost-effectiveness results are provided in Appendix J, as well as disaggregated results from the base case analysis, for costs by cost category, and costs and outcomes (life years [LYs] and quality-adjusted life years [QALYs]) by health state.

Table 81: Base-case deterministic results at list price

Technologies	Total			Incremental			ICER (£/QALY)	Net Health Benefit	Incremental NHB
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs			
DRd	[redacted]	10.760	[redacted]	-	-	-	-	[redacted]	[redacted]
IsaVRd	[redacted]	11.551	[redacted]	[redacted]	0.791	[redacted]	IsaVRd dominates	[redacted]	[redacted]

Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; ICER, incremental cost-effectiveness ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit.

Table 82. Base-case deterministic results at PAS price

Technologies	Total			Incremental			ICER (£/QALY)	Net Health Benefit	Incremental NHB
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs			
DRd	[redacted]	10.760	[redacted]	-	-	-	-	[redacted]	[redacted]
IsaVRd	[redacted]	11.551	[redacted]	[redacted]	0.791	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; ICER, incremental cost-effectiveness ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years.
Isatuximab PAS, [redacted]

B.3.10.2 *Clinical outcomes from the model*

The LYs and QALYs for both progression-free and progressed health states for the DRd and IsaVRd treatment arms, along with their incremental differences are provided in Table 83. The model results show that IsaVRd offers a clear benefit in the progression-free state, with an incremental gain of 2.236 LYs and [redacted] QALYs compared with DRd.

Table 83: Pairwise analysis: health outcomes breakdown by health state

Health state	DRd		IsaVRd		Increment	
	LYs	QALYs	LYs	QALYs	LYs	QALYs
Progression-free	7.358	[redacted]	9.594	[redacted]	2.236	[redacted]
Progressed	3.402	[redacted]	1.957	[redacted]	-1.444	[redacted]
Total	**10.760**	[redacted]	**11.551**	[redacted]	**0.791**	[redacted]

Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; LY, life years; QALYs, quality-adjusted life years.

B.3.11 *Exploring uncertainty*

B.3.11.1 *Probabilistic sensitivity analysis*

Probabilistic sensitivity analysis (PSA) was conducted to account for the statistical uncertainty of all parameters by randomly sampling from their respective probability distribution. All parameters are sampled simultaneously, and the results are recorded. Parametric survival inputs for a given survival distribution are varied jointly in a manner that accounts for the inherent relationship between them. Multivariate normal distributions are therefore assumed in PSA using the corresponding variance-covariance matrices.

The mean ICER across 1,000 PSA iterations based on list prices is shown in Table 84. A PSA convergence plot is presented in Figure 56. A cost-effectiveness acceptability curve (CEAC) is presented in Figure 57. A cost-effectiveness scatterplot is presented in Figure 58.

Table 84: Pairwise PSA results IsaVRd vs DRd

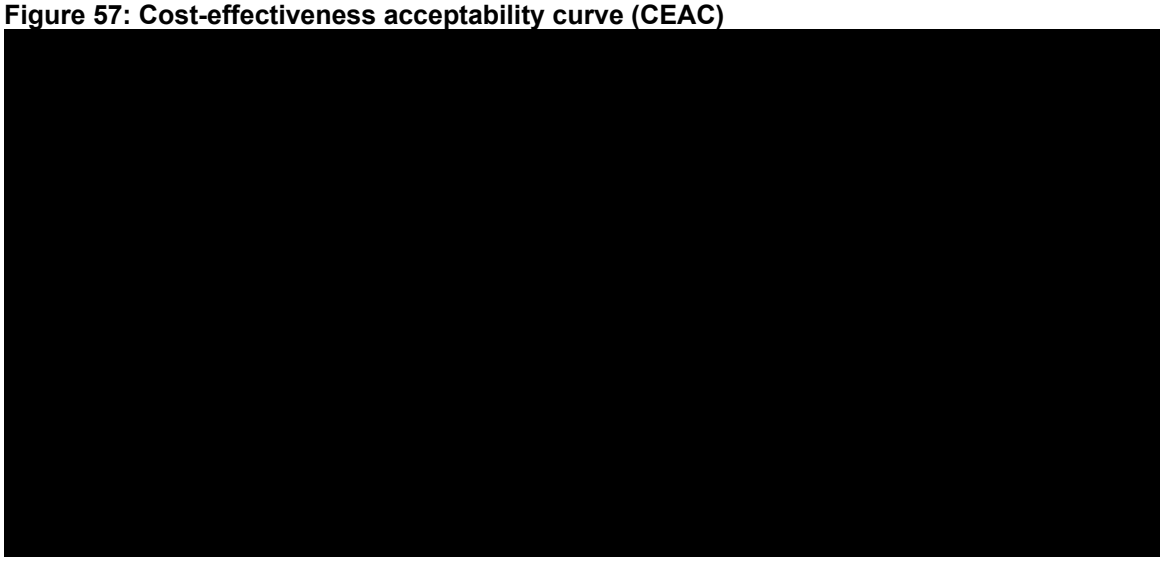
	Probabilistic mean vs DRd						
Treatment	**Total costs**	**Total LYs**	**Total QALYs**	**Incremental costs**	**Incremental LYs**	**Incremental QALYs**	**ICER**
DRd	[redacted]	10.097	[redacted]				
IsaVRd	[redacted]	10.834	[redacted]	[redacted]	0.738	[redacted]	IsaVRd dominates

Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; ICER, incremental cost-effectiveness ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; LY, life year; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 56: PSA convergence

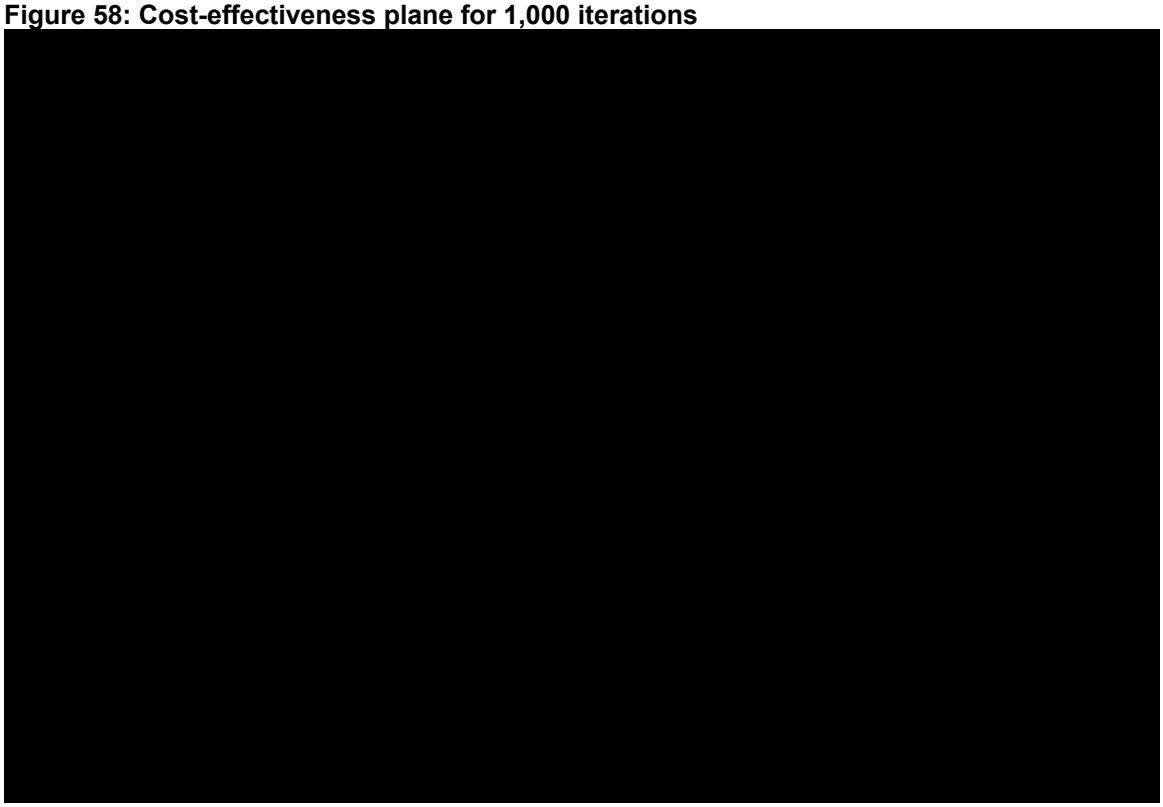
Abbreviations: PSA, probabilistic sensitivity analysis.

Figure 57: Cost-effectiveness acceptability curve (CEAC)



Abbreviations: CEAC, cost-effectiveness acceptability curve; DRd, daratumumab, lenalidomide, and dexamethasone; IVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

Figure 58: Cost-effectiveness plane for 1,000 iterations



Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; IVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; QALY, quality-adjusted life year; Rd, lenalidomide and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone; WTP, willingness-to-pay.

B.3.11.1.1 Discussion of variation between the base case and PSA results

The variation between the incremental cost-effectiveness results from the base-case analysis and the PSA demonstrates some deviations. Specifically, the incremental costs, LYs, and QALYs differ slightly between the two analyses (Table 85). These variations suggest that while the PSA provides results that are largely consistent with the base case, there is notable variability, particularly in incremental costs and ICER.

Table 85 Deviation (probabilistic minus deterministic)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
DRd	[redacted]	-0.663	[redacted]				
IsaVRd	[redacted]	-0.717	[redacted]	[redacted]	-0.054	[redacted]	-

Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; ICER, incremental cost-effectiveness ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; LY, life year; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

B.3.11.2 *Deterministic sensitivity analysis*

A deterministic sensitivity analysis (DSA) was performed by varying each input parameter as detailed in Table 79. For each parameter, bounds are calculated from the 95% confidence interval (CI) of the assigned probability distribution when available. When standard errors are not available, a 10% standard error is assumed to inform the 95% CI. Beta distributions are assumed for uncertain parameters bound by 0 and 1,

such as utilities, proportions, and probabilities. Log-normal distributions are assumed for HRs. Gamma distributions are assumed for other uncertain parameters, including various cost parameters to capture skew and avoid the need for truncation. The key model drivers will be presented in tabular form and a tornado diagram to graphically represent their effect on the overall ICER in Figure 59.

The most influential factor on the ICER for IsaVRd versus DRd was the relative dose intensity (RDI) of isatuximab IV during the continuous phase of treatment. The RDI for the induction phase of IsaVRd also had a significant impact. These results align with expectations, as RDI is a key driver of drug acquisition costs, which are among the largest component of the total costs in the model. Subsequent treatment costs for both DRd and IsaVRd, as well as patient weight and administration costs for IV and injection routes, were also notable factors. The RDI of lenalidomide during the continuous phase of IsaVRd had a moderate effect. Overall, RDI and subsequent treatment costs emerged as key drivers of the ICER.

Figure 59: ICER tornado plot from deterministic sensitivity analyses – top 10 parameters (IsaVRd vs DRd)

Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; ICER, incremental cost-effectiveness ratio; IsaRd, isatuximab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; RDI, relative dose intensity.

B.3.11.3 *Scenario analysis*

For the primary comparison with DRd, various scenario analyses were performed by modifying model assumptions or parameters. The justification for each scenario is detailed and the deterministic results of these analyses are provided in Table 86 below.

The scenario analysis illustrated the robustness of IsaVRd's cost-effectiveness profile compared with DRd across various assumptions and model inputs. In all scenarios with list price, IsaVRd consistently demonstrated cost savings, dominating DRd by providing higher QALYs at a lower cost. Changes in time horizons (from 10 to 25 years), discount rates, administration cost assumptions, and alternative models for time-to-treatment discontinuation, overall survival, and progression-free survival maintained IsaVRd's dominance. Notably, scenarios incorporating vial sharing, exclusion of drug wastage, and adjustments to relative dose intensity further reduce incremental costs, strengthening IsaVRd's economic value. Results at PAS price are based solely on the current discount for isatuximab and should be interpreted with caution until all PAS prices for comparators and subsequent treatments are incorporated into the model.

Table 86: Summary of scenario analyses

#	Scenario analysis	Rationale	With list price			With PAS price		
			Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	Base case	Base case	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
1.a	Time horizon: 10 years	Different time horizons	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
1.b	Time horizon: 20 years		[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
1.c	Time horizon: 25 years		[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
1.d	Time horizon: IMROZ RCT follow-up (5.67 years)	IMROZ maximum follow-up	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]

#	Scenario analysis	Rationale	With list price			With PAS price		
			Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
2.a	Discounting: 0%	Different discount rates	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
2.b	Discounting: 1.5%	Different discount rates	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
3	Vial sharing (exclude wastage)	Tests the impact of optimising drug use and excluding wastage to reduce treatment costs.	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
4	Admin cost applied to all components	Evaluates alternative method of costing administration costs	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
5.a	No RDI applied	Assuming 100% of doses have been taken	[redacted]	[redacted]	£5,013	[redacted]	[redacted]	[redacted]
5.b	RDI method - acquisition and administration costs	Evaluates alternative method of incorporating the RDI	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
6	Scenario 1% Dara IV	Assesses the impact of Dara IV for 1% of patients	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
7a	Subsequent treatment: Clinicians estimates	Tests the effect of using individual expert clinical opinion from England and Wales for subsequent distributions	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
7b			[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
7c			[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]

#	Scenario analysis	Rationale	With list price			With PAS price		
			Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
7d			[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
7e			[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
7f			[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
7g			[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
7h			[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
7i			[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
7j			[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
8.a	Attrition rates from Yong et al.	Same attrition rate applied to all comparators	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
8.b	Subsequent treatments: Lump sum ToT	Subsequent treatments applied after 1st line discontinuation	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
8.c	Subsequent treatments: Per cycle	Subsequent treatments cost is based on the PPS time	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]

#	Scenario analysis	Rationale	With list price			With PAS price		
			Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
9.a	OS: HR not fixed	Assumes the HR keeps improving after IMROZ follow-up for OS	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
9.b	OS: Generalised gamma	Alternative distribution for OS	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
10.a	PFS: HR fixed	Assumes the HR is fixed after IMROZ follow-up for PFS	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
10.b	PFS: Gompertz	Alternative distribution for PFS	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
10.c	PFS: Weibull	Alternative distribution for PFS	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
11.a	TTD: Gamma distribution	Alternative distribution for TTD	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
11.b	TTD: Weibull	Alternative distribution for TTD	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
11.c	TTD: HR between MAIA PFS and TTD for DRd	Evaluate alternative method to model TTD for DRd	[redacted]	[redacted]	£7,769	[redacted]	[redacted]	[redacted]
11.d	TTD = PFS	Extreme scenario to model TTD for IsaVRd and DRd	[redacted]	[redacted]	£123,416	[redacted]	[redacted]	[redacted]
11.e	Naïve TTD curve for DRd	Extreme scenario to model TTD for DRd	[redacted]	[redacted]	£28,758	[redacted]	[redacted]	[redacted]

#	Scenario analysis	Rationale	With list price			With PAS price		
			Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
11.f	TTD HR for IsaVRd versus DRd is 1	Simplified assumption of no treatment effect between IsaVRd and DRd TTD	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
12.a	Constant HR MAIC	Alternative to parametric MAIC in the base-case	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
12.b	Standard NMA	IsaVRd and VRd were extrapolated using IMROZ KMs. HR IsaVRd versus VRd is fixed for OS after IMROZ follow-up. Comparators are modelled using constant HR versus VRd.	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
13.a	Utilities: PFS model 1	Alternative model with the inclusion of Overall Response as a covariate	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
13.b	Utilities: PFS model 3	Assumes no treatment effect on PFS utilities	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
13.c	Utilities: PPS IMROZ	Alternative to literature	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]
13.d	Utilities: PPS Hatswell	Alternative source in the literature	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; DOT, duration of therapy; DRd, daratumumab, lenalidomide, and dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; IV, intravenous; m, median; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year; RCT, randomised controlled trial; RDI, relative dose intensity; TA, technology appraisal; TTD, time to discontinuation.

B.3.12 *Subgroup analysis*

There are no subgroups under consideration in this submission.

B.3.13 *Benefits not captured in the QALY calculation*

The model assumes the same post-progression utility at second, third and fourth line. This is a conservative assumption as utility is expected to decline across lines of treatment.

In addition, caregiver disutility and the societal perspective, for example work time lost in terms of absenteeism and presenteeism of both the patient and the caregiver, is not considered within the model. This could potentially represent a substantial benefit that is not captured in the QALY calculation.

B.3.14 *Validation*

B.3.14.1 *Validation of de novo cost-effectiveness analysis*

The validation process of the model is detailed in Appendix P.

B.3.14.1.1 Clinical validation

To understand the plausibility of inputs and ensure they were representative of the disease space, a series of validation exercises were completed.

The first validation meeting was with a UK clinical expert. He is a consultant haematologist with a specialist interest in myeloma and plasma cell disorders, as well as being an Honorary Associate Professor. He was able to provide valuable insight into the intricacies of myeloma and to express his expert opinion on treatment pathways, patient journeys, appropriate comparators, 1L market shares, IMROZ clinical expectations, clinical outcomes, therapy positioning, administration methods, transplant eligibility, prognostic factors, treatment effect modifiers, and subsequent treatments (100).

The first advisory board was conducted in November 2023, where Sanofi was able to speak to seven UK clinical experts in haematology and myeloma. They provided insights on the patient journey, treatment pathway, comparators, IMROZ clinical trial design, IsaVRd place of therapy.

The second advisory was conducted in July 2024 with 11 clinicians, including 10 from England and Wales. They provided insights on IMROZ clinical trial outcomes, subsequent therapies to inform the cost-effectiveness model and patient flow for the budget impact analysis. Reports for the advisory boards are available on request.

Interviews with four UK clinical experts were conducted in August and September 2024 to inform the survival extrapolation of IsaVRd and VRd for OS and PFS (136). Results have been included in the model selection for extrapolation.

B.3.14.1.2 Key outcome comparison

The model includes a comparison of clinical data for PFS and OS (Table 87). Comparisons between these should be taken as a guideline only. Key clinical outcomes

and model results were externally validated against known published sources and other available literature.

Table 87: Modelled versus reported outcomes in published literature

Treatment	Average OS (months)			Average PFS (months)		
	Model	Reported		Model	Reported	
	Median	Median	Source	Median	Median	Source
IsaVRd	[redacted]	NR	IMROZ	[redacted]	NR	IMROZ
DRd	[redacted]	90.3	Facon et al, 2021 (77)	[redacted]	61.9	Falcon et al, 2019 (148)
Rd	[redacted]	65.5	Facon et al, 2021 (77)	[redacted]	34.4	Facon et al, 2021 (77)
VMP	63.0	56.4	San Miguel, 2008*	21.2	19.3	Mateos et al, 2020 (145)
VCd	58.4	67.6	Flatiron	31.7	28.3	Flatiron

Abbreviations: NR, not reached; OS, overall survival; PFS, progression-free survival.
* Provided for context. ALCYONE trial was used for the MAIC but median OS was not reached.

B.3.15 *Interpretation and conclusions of economic evidence*

In summary, MM is a serious disease with limited curative options, becoming progressively more challenging to treat with each relapse. Each subsequent line of therapy typically leads to lower response rates and increased toxicities, significantly impacting patients' quality of life (HRQoL). For TI patients, optimising the duration of initial PFS is critical to enhance overall survival and maintain HRQoL. Despite advances in treatment, there is a substantial unmet need for therapies that can improve survival rates, delay disease progression, and provide deep and durable responses while maintaining tolerability.

The economic evaluation in this submission robustly leverages available data to assess the cost-effectiveness of IsaVRd against relevant comparators. The analysis was conducted as a cost-utility analysis (CUA) from the perspective of the NHS, incorporating comparators relevant to the MM treatment pathway. DRd was identified as the primary comparator that IsaVRd would replace based on clinical expert input. Extrapolations for OS, PFS and TTD were derived from patient-level data from the IMROZ trial for IsaVRd, with additional data for alternative regimens sourced from MAICs and IPW.

Model extrapolations have been validated through statistical and visual inspection and supported by clinical expert insights. This robust approach ensured that IsaVRd's long-term impact was accurately captured, despite inherent challenges in modelling subsequent treatments due to variability in MM therapies. One of the key points of uncertainty and usually the main driver in cost-effectiveness analyses relates to the time-on-treatment for comparators not included in the pivotal trial. This uncertainty was managed for the main comparator DRd by performing a MAIC using the published TTD

curve from the MAIA study. Results of the analysis indicated that there is no difference of treatment duration between IsaVRd and DRd despite a PFS benefit.

IsaVRd may offer psychological and QoL benefits for patients and their caregivers by reducing anxiety and sustaining hope during remission. However, the model did not capture the broader QoL impact on informal caregivers, which may further underestimate IsaVRd's overall benefit.

The results suggest that IsaVRd offers a cost-effective alternative with potential economic and clinical benefits, particularly in extending life years and improving quality-adjusted outcomes, based on the ICER. IsaVRd demonstrates cost savings and greater effectiveness vs DRd, showing cost-effectiveness dominance at list price with an additional [redacted] QALYs and cost savings of [redacted]. At current PAS price for isatuximab, IsaVRd dominates DRd with an additional [redacted] QALYs and cost savings of [redacted]. Note that actual PAS prices for other compounds are not publicly available and must be applied to generate an accurate ICER.

IsaVRd presents a key therapeutic option for TI patients with NDMM, addressing the high unmet need for effective, tolerable therapies that support prolonged remission and improve patient QoL. As validated by clinical experts, the survival benefits shown in the IMROZ study are substantial, marking IsaVRd as a potentially valuable addition to the MM treatment landscape for this patient population.

In an evolving clinical landscape, access to IsaVRd represents an essential advancement for frontline MM treatment, ensuring that the NHS remains aligned with international innovations in MM therapy.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]

Summary of Information for Patients (SIP)

31 October 2024

Template version	Date amended	Changes since previous version
2.0	Dec 2023	Clarifications made to guidance notes in section 3i regarding inclusion of statements on cost effectiveness.

File name	Version	Contains confidential information	Date
ID3981_Isatuximab in combination for untreated MM_SIP_31 October 2024 [noCON]	1	No	31 October 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

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

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

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Active ingredient: Isatuximab Brand name: SARCLISA®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Isatuximab in combination with bortezomib, lenalidomide, and dexamethasone (IsaVRd) for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT) is the indication that will be assessed by NICE.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response: Isatuximab (Sarclisa, Sanofi) does not currently have a marketing authorisation in the UK for treating untreated multiple myeloma when a stem cell transplant is unsuitable. European Medicines Agency (EMA) marketing authorisation is expected in Q1 2025. Marketing authorisation in the UK via the Medicines and Healthcare products Regulatory Agency (MHRA) is expected in Q2 2025.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response:

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

2024

- Myeloma UK – Sanofi UK was a pharmaceutical partner for the Myeloma UK London to Paris Ride 2024. Sanofi donated £33,990 to support 10 Sanofi riders to participate in the bike ride, which aims to raise awareness of myeloma, and to raise funds to advance myeloma research.
- C52 – Sanofi UK engaged C52 to attend a roundtable in relation to improving patient access to innovative medicines (£159.00).
- Leukaemia Care - Sanofi UK engaged Leukaemia Care to attend a roundtable in relation to improving patient access to innovative medicines (£108.00).

2023

- Myeloma UK – Sanofi UK was a pharmaceutical partner for the Myeloma UK London to Paris Ride 2023. Sanofi donated £27,990 to support 10 Sanofi riders to participate in the bike ride, which aims to raise awareness of myeloma, and to raise funds to advance myeloma research.
- Cancer 52 - Sanofi UK made a £10,000 contribution to the Cancer52 Corporate Supporters Programme but have no input into the programme content.

2022

- Myeloma UK - Sanofi UK was a pharmaceutical partner for the Myeloma UK London to Paris Bike Ride 2022. Sanofi UK donated £24,490 to support 10 Sanofi riders to participate in the bike ride, which aims to raise awareness of myeloma, and to raise funds to advance myeloma research.
- Myeloma UK – Myeloma UK chaired a workshop organised by Sanofi UK on combination therapies, and received £882 contribution. The aim of this workshop was to better understand the challenges around combination therapies and the views of relevant patient organisations.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

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

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

Response:

Description of the condition

Multiple myeloma (MM) is a rare and incurable blood cancer caused by a single type of plasma cell in the bone marrow. [1,2] These cancerous cells grow uncontrollably and produce an abnormal protein called monoclonal 'M' protein. MM cells have many mutations in their immunoglobulin genes.[1-3]

MM can lead to serious issues like high calcium levels, bone damage, anaemia, weakened immune system, and kidney problems. As the disease progresses, the balance between bone formation and breakdown is disrupted, leading to bone loss.[1] Patients also often experience pain, numbness, muscle weakness, and thickened blood.

Despite medical advances that makes MM treatable, it remains incurable, and with a relatively high death rate - more than 8 every day in the UK.[4] This is because MM is a progressive and relapsing disease with each period where there is no evidence of disease (remission) getting shorter, eventually leading to drug-resistance and subsequently, death.[5,6]

The standard treatment for MM is giving a high-dose of chemotherapy followed by a procedure where a patient's own healthy blood stem cells are used to replace bone marrow that has been damaged by the high dose of chemotherapy. However, about two-thirds of newly diagnosed patients will not be eligible to undergo this procedure due to age, poor health, or other medical conditions.[7,8]

Choosing the most optimal first-line treatment is essential to prolonging remission, enhancing survival rates, and improving the quality of life of patients with MM. Early and effective intervention can help mitigate the challenges associated with multiple relapses due to disease progression and treatment resistance, ultimately leading to improved outcomes.

Number of patients affected

In the UK, myeloma is the 19th most common cancer, accounting for 2% of all cancer cases. Multiple myeloma primarily affects patients aged 65–74 years.[9,10]

There are approximately 6,000 new cases of myeloma in the UK annually (an annual population incident rate of 0.013%), with 5,316 reported in England in 2022. This number is expected to rise to approximately 8,300 new cases of MM each year in 2038–2040.[11,12]

Impact on patients quality of life

MM affects both the physical and mental health of individuals living with the condition. The symptom of MM significantly reduces patients' quality of life (QoL). Studies in the UK, France, and Germany show that MM patients experience high levels of fatigue and bone pain in both early and advanced stages of the disease.[13-15] Fatigue and bone pain are strongly linked to lower health-related quality of life (HRQoL). Furthermore, patients with MM have worse HRQoL compared to those with other blood cancers like acute myeloid leukemia and Hodgkin lymphoma.[16]

Mental health is also adversely affected. An online survey in 2021 revealed that 80% of patients with MM experienced some impact on their mental health, with 30% reporting it as having a major impact.[17] In a prospective study, 37% of patients worried about their future health, 34% frequently thought about their disease, and 21% feared death.[18] In the UK, 27.4% of patients with MM showed signs of anxiety and 25.2% showed symptoms of depression.[19]

Patients who participated in choice experiments have expressed a preference for treatments that are more efficacious and are willing to tolerate increased side effects with a therapy that can provide this benefit.[20,21]

Impact on caregivers

Caregivers also face a significant QoL burden, often overlooked in HTAs. Most care is provided by family members rather than professional carers, leading to stress and anxiety that can harm the caregiver's health. A Myeloma UK study found that 94% of carers are emotionally affected, with uncertainty being a major factor, and 84% always prioritize the patient's needs over their own. About 25% of working carers had to stop working or retire early due to their caregiving responsibilities. Carers also reported a loss of control over their lives, changes in household roles, lifestyle changes, and missing important life events.[5,19,22]

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

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

Response:

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

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

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

Patients receiving isatuximab treatment should have blood tests before the first isatuximab infusion – a set of protocol that is typical for anti-CD38 drugs like isatuximab (Anti-CD38 monoclonal antibody drugs work by helping the immune system kill cancer cells).

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

2c) Current treatment options:

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

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing

current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Response:

The treatment pathway for MM in England is largely determined by recommendations made by the National Institute for Health and Care Excellence (NICE). Patients who are not eligible for transplant are able to receive treatments such as daratumumab with lenalidomide and dexamethasone (DRd), lenalidomide plus dexamethasone (Rd), thalidomide-based therapies or bortezomib-based therapies.[24,25,26]

The comparators in the final scope for this appraisal are:[27]

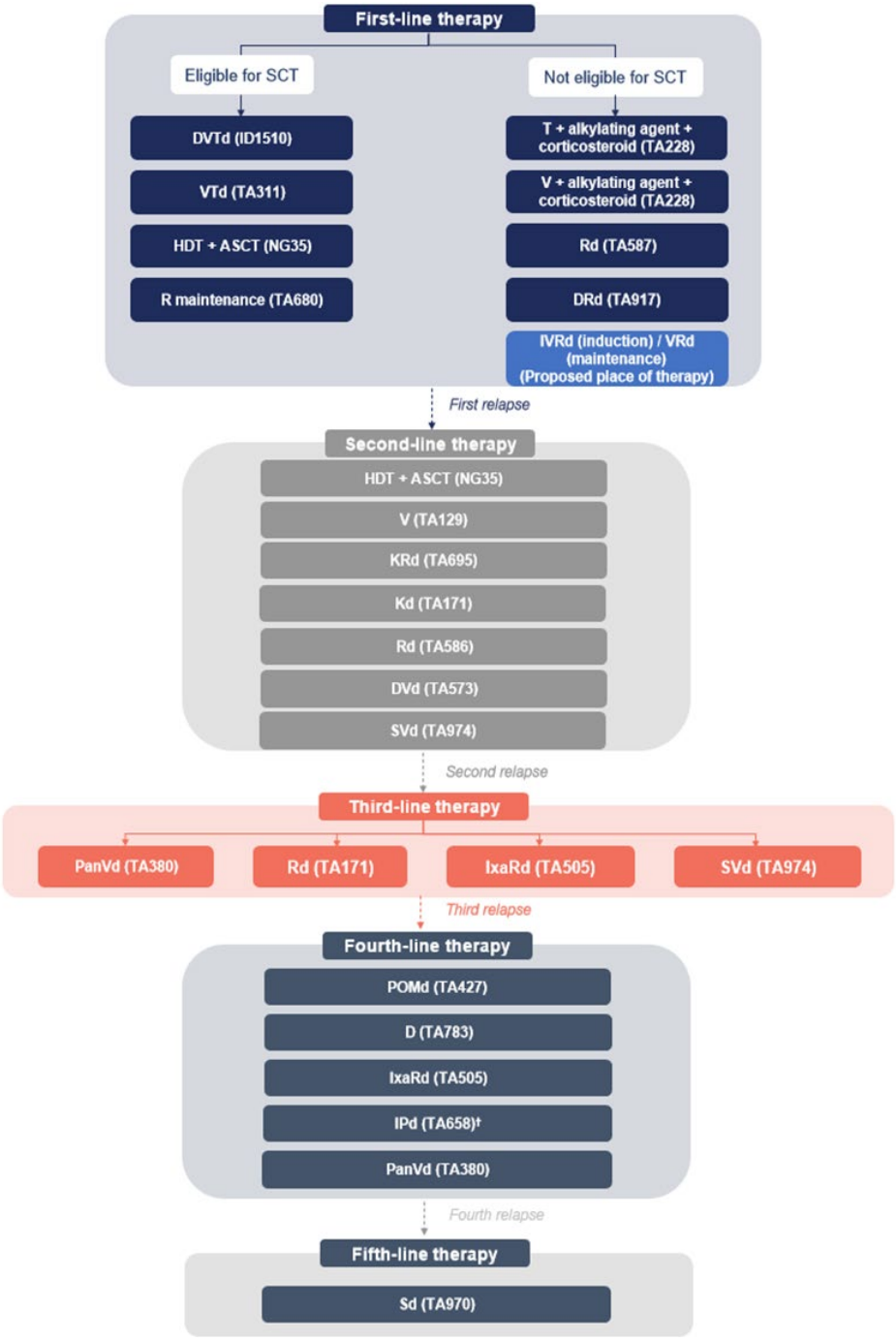
- DRd
- Rd
- Bortezomib with alkylating agent and corticosteroid (VCd and VMP)

However, it is worth noting that before the introduction of DRd, and as outlined in the final scope of TA917, the primary comparator was Rd, which accounted for approximately 70% of TI patients. According to TA917 and discussion during the decision problem meeting for this appraisal, DRd is expected to account for 65% of patients in 2024-2025 with clinicians estimating this figure to be currently as high as 80-90%, making it the main relevant comparator.

The current clinical pathway of the care for patients with NDMM in the UK, along with the proposed positioning of IsaVRd, is provided in Figure 1; the first-line treatment options for transplant ineligible patients are listed on the right-hand side of the first box in the figure 1.[28]

IsaVRd, in line with its expected licence, is a first-line treatment option for patients with NDMM who are ineligible for transplant. IsaVRd is the first of its kind and takes advantage of the individual and synergistic anti-myeloma effects of the four classes of drugs that it is made up of (anti-CD 38 [isatuximab], proteasome inhibitor [bortezomib], an immunomodulatory agent [lenalidomide] and a steroid [dexamethasone]).

Figure 1. Current NDMM treatment pathway in England, as recommended by NICE, with anticipated positioning of IsaVRd [28]



Abbreviations: ASCT, autologous stem cell transplant; CDF, Cancer Drugs Fund; d, dexamethasone; D, daratumumab; HDT, high-dose therapy; I, isatuximab; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; Ixa, ixazomib; K, carfilzomib; MM, multiple myeloma; NG, NICE Guidance; NICE, National Institute for Health and Care Excellence; Pan, panobinostat; POM, pomalidomide; R, lenalidomide; S, selinexor; SCT, stem cell transplant; T, thalidomide; TA, technology appraisal; V, bortezomib.
†Note that this represents therapies that are routinely commissioned or available in the cancer drugs fund.
Source: Adapted from NICE guideline on diagnosis and management of myeloma [NG35] and lead team presentation for daratumumab monotherapy CDF review of TA510.

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

Context:

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

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

Response:

A patient preference study was conducted involving people living with MM in the UK and aimed to understand the relative importance they place on different features of treatment such as progression-free survival and treatment toxicity.[29] Patients with MM were invited by the cancer charity Myeloma UK to participate in an online survey, and a total of 560 participants completed the survey. The study found that, on average, respondents placed most importance on increase in progression-free survival, followed by severe or life-threatening toxicity, and mild or moderate chronic toxicity. They found that those who gave more importance to severe or life-threatening toxicity over mild or moderate chronic toxicity (56% of patients) tended to be younger (≤70 years old), were working, and looking after dependent family members. These patients also experienced severe or life-threatening side effects more frequently.

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

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

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

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

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

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

Response:

Isatuximab is a monoclonal antibody which works by attaching to a protein called CD38 that is present on the surface of myeloma cells. This highlights the cell to the immune system (the body's natural defences), allowing the immune system to target and kill the myeloma cells.[30]

A summary of the products characteristics which includes this new indication is not yet available. The updated summary of the products characteristics will be available at the time of MHRA approval.

3b) Combinations with other medicines

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

- Yes / No

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

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

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

Response:

Yes, isatuximab is used in combination with bortezomib, lenalidomide, and dexamethasone. All the components of the combination are available in the UK.

Rationale for combination of IsaVRd

New treatments with better targeting and new combination approaches using multiple methods are needed to address the variety of this disease and improve patient outcomes.[31] Several three-drug regimens based on bortezomib, such as VCd, VMP, VTd, and VRd and DRd, are very effective in patients with newly diagnosed myeloma. These three-drug regimens are preferred because they have shown higher response rates and deeper responses in clinical trials and can be used for all patients, whether they are eligible for autologous stem cell transplant (ASCT) or not.

The benefit of adding isatuximab to the therapy with bortezomib, lenalidomide, and dexamethasone (IsaVRd) compared to using bortezomib, lenalidomide, and dexamethasone (VRd) alone in patients with newly diagnosed multiple myeloma (NDMM) who are not eligible for ASCT has been shown in the IMROZ study (discussed below).

Currently, VRd, the comparison treatment in the IMROZ study, is not available in the UK, even though it is a standard treatment in other countries based on several phase 2/3 studies that showed VRd was effective and well-tolerated in all newly diagnosed multiple myeloma patients, whether they are eligible for transplant or not.[33-35]

At the start of the study, VRd was the latest regimen showing a survival benefit over the current standard treatment (Rd) in a Phase 3 randomized study. Therefore, VRd has been recognized as a new standard treatment for NDMM patients not eligible for transplant and was selected as the comparator at the time of the IMROZ study design.[36-38]

3c) Administration and dosing

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

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

Response:

- Administration consists of an induction period with IsaVRd and a continuous period with IRd, bortezomib is stopped following induction period.
- Each cycle in the induction period lasts 6 weeks (42 days), with a total of four cycles planned
- After completion of Cycle 4, participants enter the continuous treatment period; each cycle lasting 4 weeks
- In both treatment periods, therapy may be stopped in case of disease progression, unacceptable AEs, patient decision

Table 1. SARCLISA dosing schedule in combination with bortezomib, lenalidomide, and dexamethasone

Isatuximab, 10 mg/kg IV infusion: Cycle 1: Days 1, 8, 15, 22, and 29 • Cycle 2–4: Days 1, 15, and 29 • Cycle 5–17: Days 1 and 15 • Cycle 18 and thereafter: Q4W	Bortezomib, 1.3 mg/m^2 subcutaneous injection: • Cycle 1–4: Days 1, 4, 8, 11, 22, 25, 29, and 32
Lenalidomide, 25 mg oral: • Cycle 1–4: Days 1–14 and 22–35 (10 mg/day for patients with CrCl ≥30 to <60 mL/min) • Cycle 5 and thereafter: Days 1–21	Dexamethasone, 20 mg IV on isatuximab infusion days, otherwise oral: • Cycles 1–4: Days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 (if ≥75 years, given on Days 1, 4, 8, 11, 15, 22, 25, 29, and 32) • Cycle 5 and thereafter: Days 1, 8, 15, and 22

The isatuximab component of the combination treatment is delivered by a healthcare professional, in an appropriate environment.

3d) Current clinical trials

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

Response:

The clinical efficacy (how well IsaVRd works) and safety of IsaVRd has been studied in one main study, IMROZ (NCT03319667).

The purpose of this phase III open-label study is to assess the clinical benefit of adding isatuximab to therapy with bortezomib, lenalidomide, and dexamethasone (IsaVRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) alone in participants with newly diagnosed multiple myeloma (NDMM) not eligible for transplant. Participants received IsaVRd or VRd for an induction period followed by continuous treatment with the IsaRd or Rd intervention. During the continuous treatment period, participants in the Rd group who have confirmed disease progression as assessed by the Investigator may crossover to the isatuximab plus lenalidomide and dexamethasone (IsaRd) combination. Adjustment analyses with and without crossover demonstrate similar benefit, suggesting that crossover (which only affects VRd study arm) did not impact the overall conclusions of the study. IMROZ looked primarily at how IsaVRd prolonged a person's progression-free survival, and consistent deep responses compared with VRd compared with people who had been randomly allocated to receive VRd only instead.
People who could participate in IMROZ were adults aged 18 years or older who were newly diagnosed and not considered for high-dose chemotherapy due to:

- Age ≥65 years; or <65 years with important comorbidities likely to have a negative impact on tolerability of high dose chemotherapy with stem cell transplant (SCT)

The study enrolled 446 participants with NDMM across 93 centres in 21 countries. Of these, 181 participants were randomised to VRd and 265 participants were randomised to IsaVRd.
The publication for IMROZ is available via this link:
https://www.nejm.org/doi/full/10.1056/NEJMoa2400712

3e) Efficacy

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

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Response:

Interim IMROZ results showed that the addition of isatuximab to a VRd regimen resulted in a statistically significant 40.4% lower risk of progression or death with a median follow-up of 59.73 months (hazard ratio [HR]: 0.596; [p<0.001]). At 60 months, the IsaVRd arm had a PFS of 63.2% vs 45.2% in the VRd arm.

Moreover, the percentage of patients with a complete response or better at 60 months was significantly higher with IsaVRd (74.7% vs 64.1% with VRd,, p=0.01), as was the percentage of patients with MRD-negative status and a complete response (55.5% vs 40.9%, [p=0.003]).

At the time of the data cut-off for PFS analysis (26 September 2023), 275 participants had discontinued study intervention (138 [52.1%] in the IsaVRd group and 137 [75.7%] in the VRd group).

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

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

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

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

Response:

In the IMROZ study, several questionnaires were used to assess the quality of life and health status of patients. These included:

- The EORTC QLQ-C30, a cancer-specific questionnaire with 30 items.
- The EORTC QLQ MY20, a myeloma-specific questionnaire with 20 items.
- The EQ-5D-5L, a general health questionnaire with 5 dimensions and 5 levels per dimension.

These tools measured disease-specific and general health-related quality of life, symptoms related to the disease and its treatment, health state utility, and overall health status.

Over 90% of participants completed the quality of life questionnaire for the first 14 cycles, and over 80% completed it at each cycle thereafter.

The Global Health Score from the QLQ-C30 remained stable from the start in both treatment groups and was not negatively affected by adding isatuximab.

Data from the EQ-5D-5L Health State Utility Index showed a trend suggesting that adding isatuximab to VRd improved patients' quality of life.

Adding isatuximab to VRd did not harm patients' quality of life, as measured by the EQ-5D-5L Visual Analogue Scale. The scores remained stable throughout treatment in both groups. There was no negative impact on quality of life from adding isatuximab when comparing both treatment groups. Similar results were seen in the EORTC QLQ measures, which also showed stable scores from the start in both groups and no negative impact from adding isatuximab.

3g) Safety of the medicine and side effects

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

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

Response:

IsaVRd was shown to have a manageable safety profile, similar to VRd. The safety profile of IsaVRd in the IMROZ trial was consistent with data form other isatuximab studies (GMMG, ICARIA, IKEMA) with no new safety signals and with a similar incidence in the two groups of serious adverse events during the treatment period and of adverse events leading to definitive discontinuation.

- In IMROZ, the most frequent adverse reactions (which may affect more than 1 in 5 people) are diarrhoea, peripheral sensory neuropathy, pneumonia, cataract, constipation, fatigue, upper respiratory tract infections, oedema peripheral, neutropenia, infusion reaction, insomnia, Covid-19, back pain, bronchitis. and asthenia.

- The most frequent serious adverse reaction was pneumonia. Adverse reactions with a fatal outcome during treatment (Grade 5 TEAEs) were reported in 11% of patients with Isa-VRd including Grade 5 infectious TEAEs occurring in 6.5% of patients.

- At the time of the data cut-off for PFS analysis (26 September 2023), 275 participants had discontinued study intervention (138 [52.1%] in the IsaVRd group and 137 [75.7%] in the VRd group).

- Permanent discontinuation of treatment because of adverse reactions was reported in 22.8% of patients treated with Isa-VRd.

- The median duration of exposure to treatment was 53 (range: 0.5 – 69) months in patients treated with Isa-VRd and 31 (range 0.6 – 67) months in patients treated with VRd.

The doctors and nurses managing treatment will closely monitor patients for response and side effects, and in some cases, treatment may be delayed or may be discontinued if the side-effect requires hospitalisation, or is life threatening.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

Response:

Disease control in the context of first-line therapy is critical in patients with NDMM newly diagnosed myeloma. Early use of efficacious regimens that include an anti-CD38 agent is warranted, given that the median progression-free survival and overall survival progressively decrease with successive treatments and the duration of response shortens with each relapse leading to higher treatment discontinuation, worsening survival and quality of life (QoL) outcomes.[39-43]

Therefore, optimising first-line treatment strategies is essential to prolonging remission, enhancing survival rates, and improving the quality of life of patients with MM. Early and effective intervention can help mitigate the challenges associated with multiple relapses due to disease progression and treatment resistance, ultimately leading to better improved patient outcomes.

IsaVRd is the first quadruplet regimen, combining four different medicines including an anti-CD38 antibody (isatuximab) and bortezomib for transplant ineligible patients. Combination therapies such as IsaVRd bring several medicines together to attack cancer cells in different ways.[44] This can make them more effective in treating the cancerous cells.[45] The inclusion of protease inhibitor for the induction phase may mean IsaVRd would also benefit patients with high risk cytogenetics or use in patients with renal impairment.

IMROZ trial showed that the addition of isatuximab to a VRd regimen led to a significant 40% lower risk of progression or death at a median follow-up of 5 years. The estimated progression-free survival at 60 months highlights the profound progression-free survival benefit with the IsaVRd regimen in patients 80 years of age or younger with previously untreated myeloma who were ineligible for transplantation. Progression-free survival with VRd was longer in this trial than in other phase 3 trials involving comparable patient populations.[35,46]

In patients with previously untreated myeloma, deep and sustained responses are associated with improved progression-free and overall survival, and MRD-negative status is an important prognostic factor.[47,48] In this trial, treatment with IsaVRd resulted in deep and sustained responses, with significant improvements in patients with MRD-negative status and a complete response and higher percentages of patients with MRD-negative status and sustained MRD-negative status for at least 12 months (at any point, in the intention-to-treat population). In addition, MRD-negative status was associated with improved progression-free survival.

The IMROZ trial showed that adding isatuximab to bortezomib, lenalidomide, and dexamethasone can delay worsening of the disease compared to receiving bortezomib, lenalidomide, and dexamethasone only. Overall, the IsaVRd safety profile was manageable and consistent with the known safety profiles of isatuximab, bortezomib, lenalidomide, and dexamethasone.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

While IsaVRd will be the first quad therapy for transplant ineligible patients in the UK, those receiving treatment with IsaVRd will need to attend the hospital to receive isatuximab as an IV infusion. This would require more hospital visits compared with current treatments which are delivered as a tablet (lenalidomide and dexamethasone) or via an injection (daratumumab subcutaneous) and can mean time out of daily activities to attend hospital appointments and may place additional burden on patients and carers.

As with all treatments there can be side-effects. However, clinical trial evidence indicate that IsaVRd has a manageable safety profile.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Response:

How the model reflects the condition

The chosen model type has been used in previous appraisals within MM. Its structure is known as the 'partitioned survival' approach, with patients able to be in health states that are relevant to MM:

- Progression-free (on-treatment or off-treatment)
- Post-progression (on-treatment or off-treatment)
- Death.

At the start of the model, all patients are in the progression-free state and on treatment. However, over time the disease can worsen (some patients may relapse) and they move to the post-progression state where they receive further lines of therapy for their disease, or they may die at any point during their treatment journey.

The proportion of patients in each health state is defined by three curves representing the following:

- Overall survival curve – the percentage of patients alive
- Progression-free survival curve – the percentage of patients alive without disease progression
- The difference between the overall survival and progression-free survival curves – the percentage of patients whose disease has progressed and may be receiving other therapies.

Modelling how treatment extends life

Treatments extend life by slowing disease progression and potentially increase overall survival relative to the comparators. The IMROZ trial followed patients for over 5 years, however, some patients in the clinical trial are still on treatment and are alive. Therefore, most recently available data from the trial needed to be extrapolated for a patient's lifetime. In line with NICE requirements for cost-effectiveness modelling, outcomes must be evaluated over the life-time of

the patients initiated on IsaVRd or the comparators. Statistical modelling techniques are used to estimated the impact of each treatment on health outcomes until death.

Modelling how much a treatment improves quality of life

The model assigns values (called utility values) to progression-free and post-progression health states to represent a patient's QoL. These values, between 0 and 1 (0 representing death to 1 representing perfect health), indicate how patients feel about their overall health at each phase of their treatment journey. These values for IsaVRd came from data collected during the IMROZ trial for patients.

Modelling how the costs of treatment differ with the new treatment

Time to discontinuation data from IMROZ to estimate the duration of treatment associated with IsaVRd. For comparators, data are sourced from published literature on duration of treatment. IsaVRd is associated with an increase in costs for the NHS compared with comparators. Due to the IV administration of isatuximab, there will also be additional costs for the NHS compared to current standard-of-care therapies, such as those administered orally. However, in the economic model, costs are offset against the benefits achieved to result in a summary measure of value (ICER) which will be used to determine whether IsaVRd can be reimbursed in the NHS.

Uncertainty

As not all patients were followed up until death in the IMROZ trial, long-term predictions of overall survival, progression-free survival, and time to discontinuation for IsaVRd and the comparators have been estimated beyond the trial follow-up period (i.e. extrapolated). These predictions are uncertain and as a result, different predictions have been considered and tested.

Another source of uncertainty are the outcomes for the comparison with the different comparators defined in the NICE scope. There are no clinical studies that directly compared IsaVRd to any comparators in the same study. Instead, an indirect analysis was conducted. For the comparison to DRD, RD, VMP a Matching-Adjusted Indirect Comparison was performed using comparable trials for each comparator. A MAIC is a method used in health economics and outcomes research to compare the effectiveness of different treatments when direct head-to-head clinical trials are not available. In essence, MAIC helps researchers make more accurate comparisons between treatments using existing data, which can be very useful for making informed healthcare decision.

For the comparison to VCd, no published study comparable to found. Instead, individual patient level data were available from a US claims database on VCd. This enabled a method called IPW to be used to assess comparative effectiveness of IsaVRD to VCd. Inverse Probability Weighting (IPW) is another statistical technique used to create a weighted sample that corrects for selection bias when individual patient level data are available.

Cost-effectiveness results

The cost-effectiveness is highly reliant on the confidential discounts in place for all the comparators.

The true cost-effectiveness of IsaVRd is not known because there are agreed discounts available to the NHS for comparators and other treatments used in the economic model. These discounts are not known to Sanofi. However, the NICE committee will be able to consider the cost-effectiveness results with confidential discounts applied in their deliberations.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:

IsaVRd will, if reimbursed, be the first quadruplet therapy that combines an anti-CD38 drug with all the current standard of care treatment classes, leveraging the known synergistic benefit of the different classes in treating NDMM. This represents a step-change in the management of NDMM where a key aim is to maximise benefit as early as possible in the pathway. The progression-free survival time reported in IMROZ is the longest seen in any transplant ineligible patient population study to date.[49]

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Response:

Patients eligible for transplant currently benefit from the quadruplet induction therapy of daratumumab with bortezomib, thalidomide and dexamethasone (DVTd) (TA763). In contrast, patients who are ineligible for transplant don't do not have access to the benefits of a quadruplet, induction-type therapy before transitioning to reduced maintenance or continuous therapy. Access to IsaVRd therapy for non-transplant eligible patients would help mitigate this inequality.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Response:

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

Confidence interval (CI): A range of values that you can be 95% certain contains the true mean of the population.

Clinical trial/clinical study: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease.
Incremental cost-effectiveness ratio (ICER): The ICER is the difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest.
NICE: The National Institute for Health and Care Excellence. An independent organisation set up by the government to decide which drugs and treatments are available on the NHS in England.
Quality of life: A measure of the overall enjoyment and happiness of life including aspects of an individual's sense of well-being and ability to carry out activities of daily living.
Quality adjusted life years (QALYs): QALYs are an overall measure of health outcome that weight the life expectancy of a patient with an estimate of their HRQoL (measured on a 0–1 scale).
Standard-of-care: Treatment that is accepted and widely used by medical experts and healthcare professionals for a certain type of disease.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]

Clarification questions

January 2025

File name	Version	Contains confidential information	Date
ID3981 isatuximab for MM EAG clarification_to PM for company_24 Jan2025_[CIC_Redacted]	1.0	No	16 May 2025

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

A1. The NICE scope describes the population as patients with untreated multiple myeloma who are unsuitable for stem cell transplant. In the CS, the population of interest is described as patients who are ineligible for autologous stem cell transplant. Does the company consider that there is a difference between patients 'unsuitable for' and patients 'ineligible for' stem cell transplant?

Answer: The words 'unsuitable' and 'ineligible' are used interchangeably in the CS. Although 'unsuitable' is used in the NICE scope document, 'ineligible' is employed in the label in the positive opinion issued by the Committee for Medicinal Products for Human Use (CHMP) for the EU and in the proposed MHRA label. 'Ineligible' for transplant is also a widely published and accepted term in the myeloma clinical and academic community. Therefore 'ineligible' has been used in the CS for company content alignment purposes. However, this difference is highly unlikely to affect how clinicians identify patients for treatment with IsaVRd.

A2. Patients with a diagnosis of amyloidosis were excluded from the IMROZ trial (CS, Table 8). Please clarify whether this exclusion applies to primary amyloidosis, multiple myeloma with amyloidosis, or both?

Answer: As patients with any diagnosis of amyloidosis were not eligible for inclusion in the IMROZ clinical trial, patients with primary amyloidosis or MM with amyloidosis were excluded.

A3. Please provide a clinical rationale to explain why TTD appears to be slightly longer for patients treated with DRd compared to patients treated with IsaVRd (CS, Figure 24) whereas PFS appears to be longer for patients treated with IsaVRd than for patients treated with DRd (CS, Figure 23).

Answer: As proven in the IMROZ clinical, IsaVRd was more effective than VRd (mPFS not reached vs 54.3 months, HR for disease progression or death, 0.60; 98.5% CI,0.41 to 0.88; P<0.001). The longer PFS observed for IsaVRd is attributed to the significant deep responses and MRD negativity rates, particularly sustained MRD negativity, achieved in comparison to the triplet control arm. Thus, highlighting the key contributing factor for the difference in longer PFS between IsaVRd and DRd. The addition of bortezomib during the 6-month induction phase is the only difference to DRd, and hence adds to the proven and increasing body of evidence that quadruplet regimens continue to do better than triplets in newly diagnosed patients (irrespective of receiving a transplant).

Published TTD appears to be slightly longer for patients treated with DRd compared to those treated with IsaVRd. The MAIC suggests a small numerical increase in the hazard of treatment discontinuation for IsaVRd compared to DRd, with a HR of [redacted]. However, the analysis concluded that TTD is very similar between the two regimens. The similarity in TTD can be explained by the fact that both regimens use similar drug combinations during the maintenance phase (which constitutes the largest part of the treatment timeline). Both IsaRd and DRd include an anti-CD38 monoclonal antibody, lenalidomide, and dexamethasone, leading to comparable tolerability and similar TTD outcomes. Additionally, the quadruplet regimen during the induction phase of IMROZ did not result in a difference in TTD, suggesting that the tolerability profile of IsaVRd during the induction phase is similar to DRd. Adding 4 cycles of bortezomib had little impact on TTD.

In conclusion, the 6-month induction phase of IsaVRd that encompasses multiple anti-myeloma mechanisms followed by continuous IsaRd, significantly enhanced PFS without affecting tolerability, leading to similar duration of treatment to DRd (1, 2).

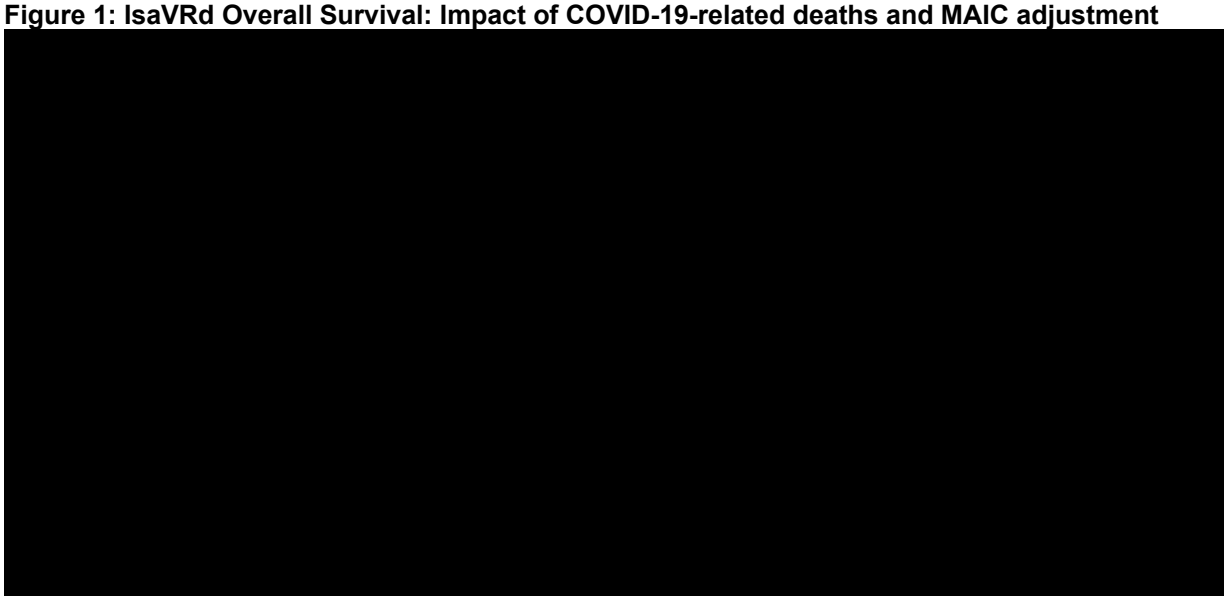
A4. The data presented in CS, Figure 23 suggest that, for patients treated with IsaVRd and DRd, mortality rates will be equal for the first 12 months, higher for patients treated with DRd between months 12 and 24, and higher for patients treated with IsaVRd between months 24 and 36, before becoming equal again from month 36 onwards. Please provide a clinical rationale to explain the apparent fluctuation in the HR that supports these differences over time being more than a statistical artefact.

Answer: The increase in mortality for patients treated with IsaVRd is largely attributed to the 12 COVID-19-related deaths recorded in the IMROZ clinical trial. In contrast, no COVID-19-related deaths were recorded in the MAIA clinical trial, as it was conducted prior to the pandemic.

Figure 1 superimposes the scenario analysis conducted in the CSR (Figure 25), in which patients with COVID-19-related deaths were censored, onto Figure 23 of the CS, which shows the IsaVRd overall survival (OS) before and after matching (MAIC) with the DRd arm from the MAIA trial. On this figure, the drop in survival after 24 months of follow-up is attributed to the 12 COVID-19-related deaths (from the curve in which COVID-19-related deaths were censored to the ITT curve). This drop has been amplified by the MAIC (from the ITT curve to the curve after matching). This is expected because the MAIC analysis assigned more weight to the most vulnerable patients, to better reflect the less fit population in the MAIA trial, and who were more likely to die from COVID-19.

In a scenario in which COVID-19-related deaths had not occurred in the IMROZ trial, as was the case in the MAIA trial, the survival of IsaVRd after MAIC would not have been attenuated as much and is expected to have remained completely differentiated from the DRd OS curve.

Figure 1: IsaVRd Overall Survival: Impact of COVID-19-related deaths and MAIC adjustment



Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; ITT, intent-to-treat; MAIC, matching-adjusted indirect comparison.

Indirect treatment comparisons

A5. In Appendix D.3.2.1 (CS, p143), the company states that, "a total of nine variables were identified and considered for adjustment".

a. Please clarify the approach adopted by the company to identify and classify prognostic factors and treatment effect modifiers

Answer: The following sources were used to identify prognostic factors and treatment effect modifiers:

- Clinical expertise – consultations with clinicians indicated that the following characteristics were prognostic and/or effect-modifying for OS and PFS (ranked by clinicians in descending order of importance): age, frailty, ISS stage, cytogenetic risk, ECOG PS, LDH levels, and renal impairment
- Patient-level data analyses of the IMROZ data to identify treatment effect modifiers:
    - PFS subgroup analyses conducted in IMROZ showed some evidence of a difference (p-value <0.1) in the treatment effect across two subgroups: MM type IgG and chromosomal abnormality 1q21+

  - OS subgroup analyses of IMROZ indicated there was some evidence of differences (p-value < 0.1) in the treatment effect in age and cytogenetic abnormality 1q21+ subgroups

- Patient-level data analyses of the IMROZ data to identify prognostic factors – Cox PH models fitted to the IMROZ patient-level data indicated that ISS stage, chromosomal abnormality 1q21+, LDH levels, and creatinine clearance had a statistically significant effect (p-value <0.1) on PFS outcomes, and ISS stage had a statistically significant effect (p-value <0.1) on OS
- Patient-level data analyses of Flatiron data – Cox PH models fitted to the Flatiron data identified age, ECOG PS, ISS, cytogenetic risk, and chromosomal abnormality 1q21+ as potential prognostic factors for OS; and ISS stage, cytogenetic risk, and chromosomal abnormality 1q21+ as potential prognostic factors for PFS

Overall, nine patient characteristics were identified as potential prognostic factors and/or effect modifiers: age, frailty, ISS stage, cytogenetic risk, ECOG PS, LDH levels, creatinine clearance (proxy for renal impairment), chromosomal abnormality 1q21+ and MM type IgG.

b. Please comment on the likely biases arising from excluding frailty, chromosomal abnormality 1q21 and LDH from the ITCs

Answer: The exclusion of frailty, chromosomal abnormality 1q21, and LDH levels from the ITCs arises due to lack of reporting in the MAIA and ALCYONE trials, which prevented adjustment for these factors in the MAICs for DRd, Rd or VMP. However, the impact of missing these factors was mitigated by adjusting for other matching characteristics, such as age, ECOG PS, and cytogenetic risk:

- Frailty: Although frailty was not explicitly accounted for, it is often defined based on a combination of factors such as age and ECOG performance status (PS), which were included in the matching process. Therefore, adjusting for these characteristics helps reduce the potential bias due to the lack of frailty data.

- Chromosomal Abnormality 1q21+: Since chromosomal abnormality 1q21+ is classified as high-risk by the International Myeloma Working Group (IMWG),

the exclusion of this factor was addressed by adjusting for differences in high cytogenetic risk, which captures some of the high-risk characteristics related to 1q21+ abnormalities.

- LDH Levels: Clinicians ranked LDH levels as having lower importance for matching, so the potential bias resulting from not adjusting for LDH was expected to be minimal. Given this clinical perspective, the exclusion of LDH is unlikely to introduce significant bias into the analysis

Overall, while the exclusion of these factors may introduce some potential for bias, the adjustments for other relevant characteristics help mitigate their impact

A6. Please confirm whether there were any differences in the PFS assessment definitions between any of the studies included in the ITCs (including trials evaluated in the NMAs and/or population-adjusted ITCs, including the Flatiron data source).

Answer: The PFS definitions from clinical studies and the Flatiron data source are summarised in Table 1. Across most trials in the evidence base, PFS was defined as the time from the date of randomisation to either progressive disease or death (which ever came first). HOVON49 and Real MM did not report a PFS definition. UPFRONT and VISTA included relapse in their definition of PFS, which was considered equivalent to disease progression as advised by clinical feedback. PFS was centrally assessed in IMROZ, MAIA and FIRST, and investigator assessed in VISTA. PFS assessor was not reported for any other trials or in the Flatiron data source.

Table 1: Summary of PFS definitions from clinical studies

Study	PFS definition	Assessor
IMROZ	The time from the date of randomisation to the date of first documentation of progressive disease (as determined by the IRC), or the date of death from any cause, whichever occurs first. Progressive disease will be assessed as per IMWG response criteria.	Centrally assessed
MAIA	Time from the date of randomisation to either progressive disease or death, whichever occurred first.	Centrally assessed
ALCYONE	Duration from the date of randomisation to either progressive disease or death, whichever came first. Progressive disease will be assessed as per IMWG response criteria.	NR

Flatiron data source	Defined as the time from treatment initiation to first progression event or death. Progressive disease assessed as per IMWG response criteria.	NR
ECOG E1A06	Time from randomisation to the earliest documentation of disease progression or death from any cause without regard for timing of disease evaluation.	NR
FIRST	Time from randomisation to disease progression (IMWG criteria) or death from any cause.	Centrally assessed
HOVON49	NR	NR
HOVON87/NMSG18	Progression-free survival was calculated until the date of disease progression, death from any cause during treatment, or data censoring at the last date on which the patient was known to be free of disease progression. Response criteria: IMWG.	NR
IFM 01/01	Progression-free survival was calculated from random assignment to progression or death. Data on patients who had not experienced disease progression were censored on the last date they were known to be alive and progression-free.	NR
MYELOMA IX	Time from randomisation to the time of progression or death.	NR
OCTANS	The duration from the date of randomisation to either progressive disease or death, whichever came first.	NR
Real MM	NR	NR
Sacchi 2011	PFS was defined from the date of being randomly assigned to the date of disease progression, date of last observation, or death from any cause.	NR
SWOG S0777	Time from the date of registration to date of first documentation of progression or symptomatic deterioration, or death due to any cause, assessed up to 6 years.	NR
UPFRONT	Time from randomisation to date of progression, relapse, or death, whichever came first.	NR
VISTA	The time between randomisation and either disease progression or relapse from complete response by EBMT criteria, or death due to any cause, whichever occurred first.	IA

Abbreviations: IA, Investigator Assessed; EBMT, European Group for Blood and Marrow Transplantation; IMWG, International Myeloma Working Group; IRC, independent review committee; MM, multiple myeloma; NR, not reported; PFS, progression-free survival.
Notes: * definition extracted from an earlier publication.

A7. The IMROZ trial includes treatment switching. Please confirm whether any of the other studies included in the NMAs were affected by treatment-switching or crossover.

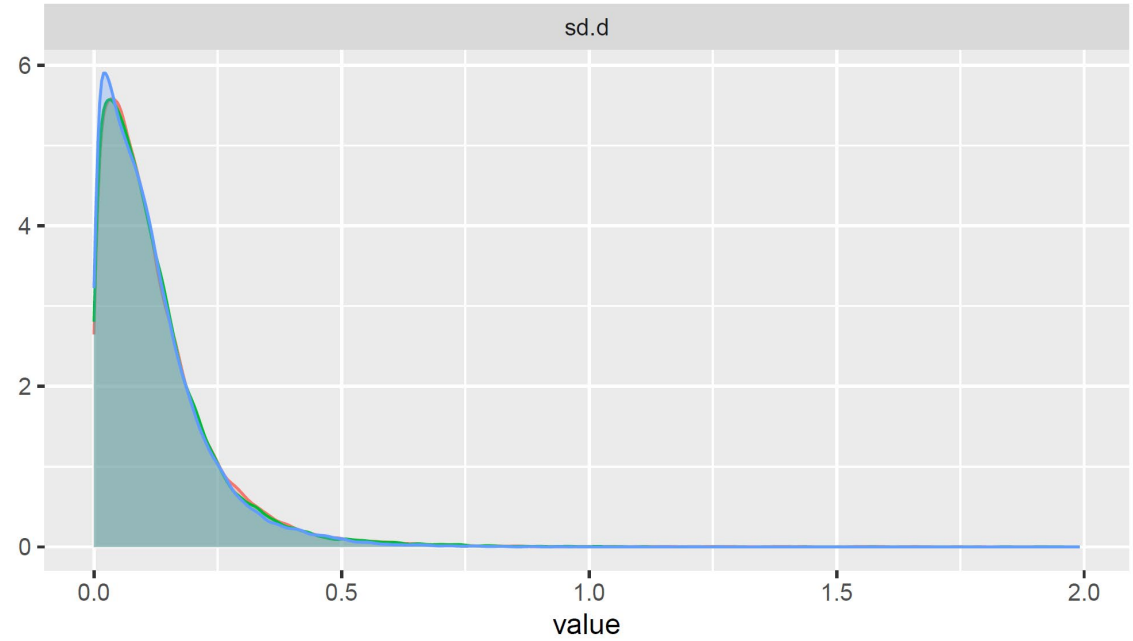
Answer: One other trial in the evidence base permitted crossover to the experimental treatment arm – Beksac 2011 (MP versus MPT, included in the NMA of

OS only). Crossover from the MP arm to the MPT arm was allowed in cases with progressive or stable disease after a minimum of 3 months of treatment with MP. Of the 62 patients in the MP arm of Beksac 2011, eight patients (13%) crossed over and received MPT. Given the low proportion of patients who received MPT following crossover, the impact of crossover in Beksac 2011 on the NMA was expected to be minimal.

A8. In the NMAs, please comment on whether Bayesian updating was observed in the random-effects model using a Uniform (0,2) prior distribution for the between-study SD. Please also provide the posterior density plot for the between-study SD.

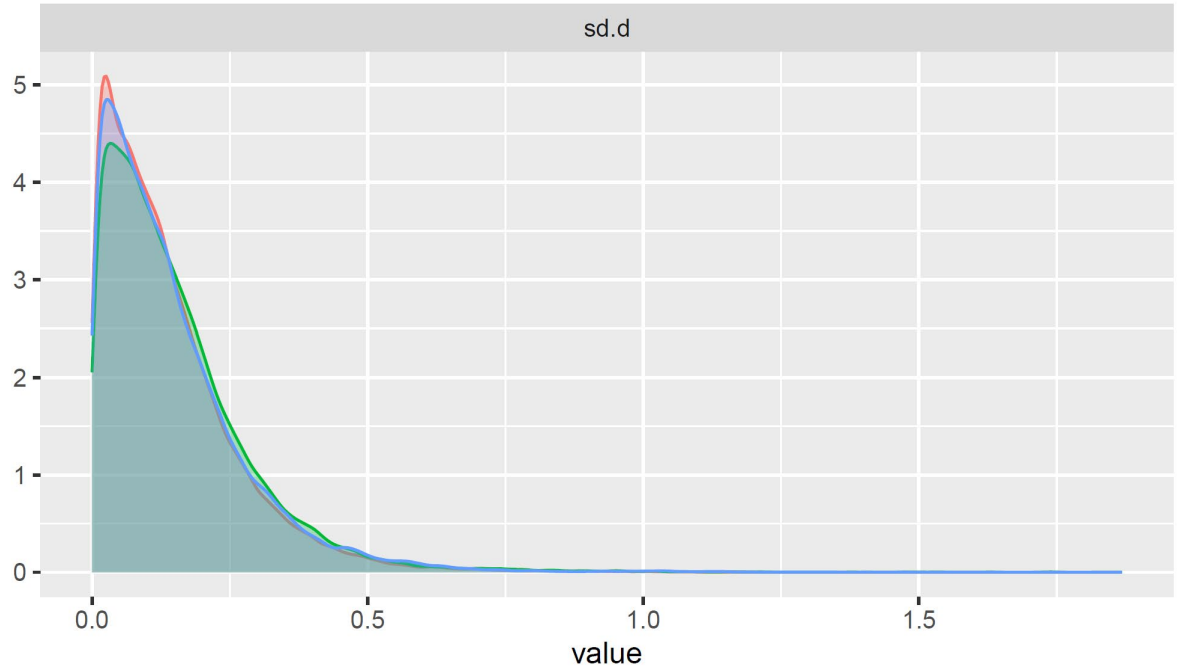
Answer: The posterior density plots for the between-trial SD in the random-effects models using a Uniform (0,2) prior distribution are presented in Figure 2 and Figure 3. For both OS and PFS, the posterior density does not represent a Uniform (0,2) distribution, confirming that Bayesian updating was observed.

Figure 2: Posterior density plot for the between-trial SD – PFS NMA



Abbreviations: NMA, network meta-analysis; PFS, progression-free survival; SD, standard deviation.
Note: Three chains were used in the analysis (represented by the three colours).

Figure 3: Posterior density plot for the between-trial SD – OS NMA



Abbreviations: NMA, network meta-analysis; OS, overall survival; SD, standard deviation.
Note: Three chains were used in the analysis (represented by the three colours).

A9. Regarding the ITCs, the company states, "an approach that relaxes the PH assumption is preferred and used in the base case" (CS, Section 3.3.2.3, p137). Please confirm why time-varying HRs were used in the base case despite stating that "[redacted]" based on the Schoenfeld global test of proportionality (CS, Appendix D.3.2.2.6, Table 49).

Answer: The assessment of proportional hazards is subjective and relies on several elements, including visual inspection of Kaplan–Meier curves, log-cumulative hazard curves, Schoenfeld residual plots; and the Schoenfeld global statistical test of proportionality. In most cases, there was some evidence against the proportional hazard assumption such as non-parallel and/or crossing of log-cumulative hazard curves, and/or curved smoothed lines in the Schoenfeld plots. However, the Schoenfeld global test did not show statistical significance (p-value>0.05) in any case. It is important to emphasise that a non-significant p-value does not confirm the null hypothesis of proportional hazards but rather indicates insufficient evidence to reject it. Given that all log-cumulative hazard curves crossed and/or were not parallel for IsaVRd versus comparators, both for OS and PFS, the base case analysis adopted an approach that relaxes the strict PH assumption. This method allows

flexibility to model either a time-varying hazard ratio (HR) or a reasonably constant HR, depending on the data. To ensure robustness, constant HR assumptions were also explored in a scenario analysis, which yielded consistent conclusions with the base case. This dual approach enhances the reliability of the findings while addressing potential deviations from proportional hazards.

A10. The company states that the first step in the time-varying HR approach was to "fit a weighted parametric survival model for each of the seven standard distributions" (CS, Appendix D.3.2.1, p145).

a. Please confirm how the weights were derived and how they were incorporated into the parametric models

Answer: The weights used in the time-varying HR approach were derived from the MAIC/IPW analysis and applied to the parametric models using the weights argument in the flexsurvreg function from the flexsurv package. These weights, representing the inverse probability of selection for each patient, were incorporated into the likelihood function during model fitting, as recommended in NICE TSD 17-18. In both the MAIC and IPW analyses, weights were assigned to patients in the IsaVRd arm to align their baseline characteristics with those of the comparator groups. In the MAIC analysis, the weights matched IsaVRd patients to the aggregated data of DRd, Rd, and VMP, while in the IPW analysis, weights were applied to IsaVRd patients to adjust for differences in baseline characteristics relative to the VCd group.

b. Please confirm which comparators were investigated using a time-varying HR ITC approach, and whether IsaVRd and the comparator arm under investigation were modelled separately.

Answer: The time-varying HR ITC approach was applied to all relevant comparators in the UK including DRd, Rd, VMP and VCd, and was assessed through MAIC/IPW. For a given comparison (e.g. IsaVRd versus DRd), parametric survival models were fitted to data for both treatments in a single analysis using a multivariate treatment effect parameter. Relative effects were applied to the shape and scale parameters, allowing the derived relative treatment effect (i.e. the HR) to vary over time. The comparator arm under investigation in the IMROZ trial is VRd and is modelled

independently to IsaVRd in the model. However, it is not available in NHS practice and thus is not considered a relevant comparator.

A11. For the comparison between IsaVRd and VCd using Flatiron data:

a. Please provide a rationale for using the IPW approach

Answer: The IPW approach was chosen because it allowed for more precise population-adjusted indirect comparisons, given the availability of patient-level data (PLD) for both IsaVRd (from IMROZ) and VCd (from the Flatiron data source). Additionally, none of the 28 observational studies and non-RCTs investigating VCd identified from the clinical SLR were deemed suitable for unanchored MAIC (which would be required given studies were observational or non-randomised) due to the reasons in Table 2. The benefits and limitations of the methods described in NICE DSU TSD 17 were assessed. Among the available methods, propensity score matching and inverse probability weighting (IPW) were considered the two most widely accepted for population adjustment. IPW was preferred because it utilises all of the available patient data, whereas propensity score matching reduces the sample size by discarding unmatched data. When PLD was available for both arms, imputation methods could be used to address missing baseline characteristics in the comparator data, enabling a more accurate specification of the propensity score model. In contrast, when only aggregate data were available for the comparator population, imputation methods were infeasible. This limitation could lead to the omission of summary characteristics with a high level of missing data (e.g., >10%), potentially introducing additional bias due to unmeasured confounding.

Table 2: Summary of excluded non-RCTs and observational studies

Study	Treatment(s)	Study country	Sample size*	Reason for exclusion
Ailawadhi 2023 (3)	VCd	NR	35	Study country not reported, no baseline characteristics reported
Al Saleh 2021 (4)	VCd	US	62	No baseline characteristics reported
Barth 2021 (5)	VCd	US	444	Important prognostic factors were not reported
Chan 2019 (6)	VCd	New Zealand	155	No relevant outcome data reported
Chari 2019 (7)	VCd, VRd	NR	146	Study country not reported, only two baseline characteristics reported, no relevant outcome data reported

Study	Treatment(s)	Study country	Sample size*	Reason for exclusion
Chen 2022 (8)	VCd > T	China	56	Conducted in China
Demisroy 2022 (9)	VCd	Turkey	35	No baseline characteristics reported, no relevant outcome data reported, conducted in Turkey
Hari 2019 (10)	VCd	US	749	High levels of missing data in reported baseline characteristics and important prognostic factors were not reported
He 2021 (11)	VCd, VRd	US	1,225	Minimal baseline characteristics reported
Huang 2014 (12)	VCd > T	NR	175	Study country not reported, minimal baseline characteristics reported
Jiminez-Zepeda 2015 (13)	VCd	NR	91	Study country not reported, minimal baseline characteristics reported
Jimenez-Zepeda 2017 (14)	VCd	Canada	42	Small sample size and important prognostic factors were not reported
Jimenez-Zepeda 2021 (15)	VCd/P	Canada	562	High levels of missing data in reported baseline characteristics
Liapis 2021 (16)	VCd	NR	99	Study country not reported, no relevant outcome data reported
Martinez-Cordero 2021 (17)	VCd	Colombia	NR	Investigated mixed transplant population; 64% of patients did not receive SCT; however, it was unclear whether enrolled patients were transplant-eligible or -ineligible, no baseline characteristics reported for non-transplant population, conducted in Colombia
Nakatazo 2021 (18)	VCd > VTd	Japan	51	Conducted in Japan
Nie 2022 (19)	VCd > V	Canada	70	Treatment regimen not considered representative of clinical practice
Rampotas 2021 (20)	VCd	UK	158	High levels of missing data in reported baseline characteristics
Sandecká 2021 (21)	VCd	Czech Republic	377	Minimal baseline characteristics reported
Schutz 2020 (22)	VCd	Argentina	55	Investigated mixed transplant population, no baseline characteristics reported for non-transplant population, conducted in Argentina
Shimura 2023 (23)	VCd	Japan	71	Conducted in Japan
Stork 2019 (24)	VCd	Czech Republic	47	Conducted in Czech Republic
Tang 2017 (25)	VCd	China	34	Conducted in China
Tuchman 2017 (26)	VCd	US	14	Small sample size

Study	Treatment(s)	Study country	Sample size*	Reason for exclusion
Uttervall 2019 (27)	VCd	Sweden	213	Minimal baseline characteristics reported and high level of missingness in those reported. The subgroup of non-transplant patients would be used as a proxy for transplant-ineligible patients
Vallente 2022 (28)	VCd	Philippines	26	No baseline characteristics reported, conducted in Philippines
Wang 2017 (29)	VCd > T	China	32	Conducted in China
Zhao 2022 (30)	VCd, Rd	Australia/ New Zealand	583	Some baseline characteristics were reported; however, there is a high level of missingness for ECOG PS, and a substantially higher proportion of patients with ISS Stage III compared with IMROZ

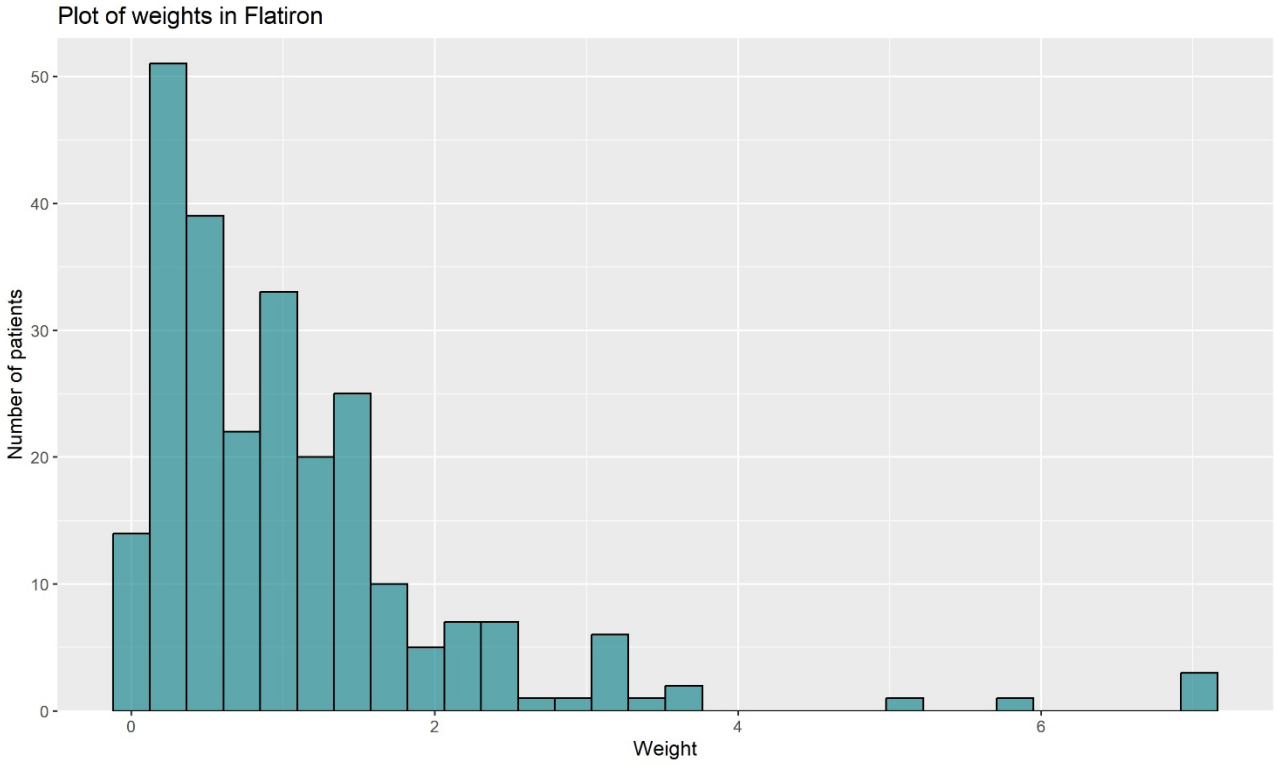
Key: ECOG PS, Eastern Cooperative Oncology Group Performance Status; ISS, International Staging System; NR, not reported; Rd, lenalidomide and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone; SCT, stem-cell transplant; T, thalidomide; VCd, bortezomib, cyclophosphamide, and dexamethasone; VTd, bortezomib, thalidomide, and dexamethasone.

Note: * Sample size reported for VCd-treated patients.

b. Please provide the distribution of propensity scores obtained from the IPW analysis

Answer: The distribution of propensity scores obtained from the IPW analysis is presented in Figure 4.

Figure 4: Rescaled weights for VCd (with trimmed weights)



Abbreviations: VCd, bortezomib, cyclophosphamide, and dexamethasone.

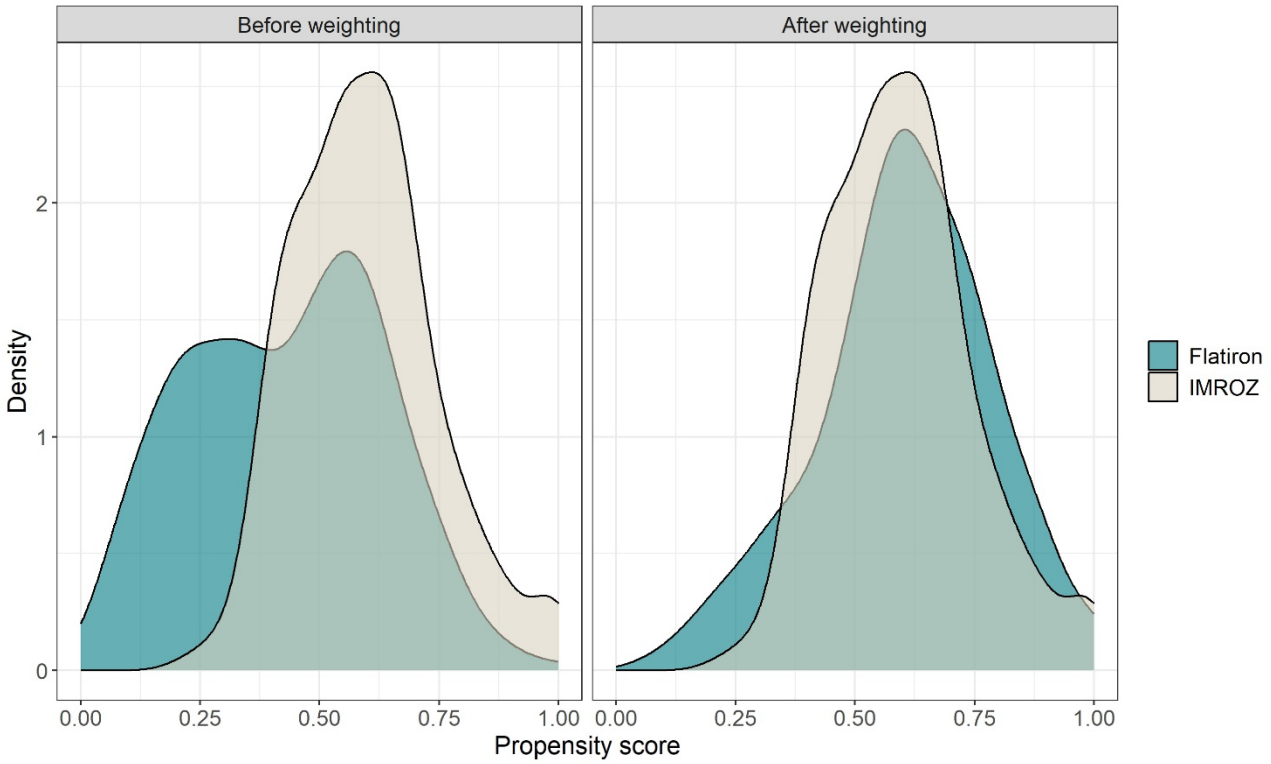
c. The company states, "in some cases, VCd-treated patients were assigned extreme weights" (CS, Appendix D.3.2.2.9, p175). Please provide more information, including the proportion of VCd-treated patients who were assigned extreme weights.

Answer: Following the IPW process, trimming was applied to the weighted data. The greatest 1% of weights (n=2) were set to the 99th percentile of the distribution of the weights. The two greatest weights (8.3 and 559.5) were thus set to 7.1.

d. Please provide a plot of the absolute SMDs, both pre- and post-weighting, for all factors included in the IPW analysis.

Answer: A propensity score density plot for VCd is presented in Figure 5. Unweighted and weighted characteristics are provided in Table 3.

Figure 5: Propensity score density plot – VCd



Abbreviations: VCd, bortezomib, cyclophosphamide, and dexamethasone.

Table 3: Table of unweighted and weighted characteristics – IMROZ, VCd

Characteristic	IMROZ (IsaVRd)	Flatiron VCd (filtered)	SMD before weighting	IMROZ (IsaVRd)	Flatiron VCd weighted* (filtered)	SMD after weighting
N/ESS	265	249		265	122.83	
Age (mean (SD))	71.68 (4.03)	67.16 (8.99)	0.649	71.68 (4.03)	72.96 (6.35)	0.239
Gender male, n (%)	143 (54.0)	159 (63.9)	0.202	143 (54.0)	78.8 (64.2)	0.209
TT TRT from diagnosis (mean (SD))	2.05 (3.71)	1.14 (1.16)	0.332	2.05 (3.71)	1.80 (2.30)	0.080
Missing, n (%)	2 (0.75)	0 (0.0)		2 (0.75)	0 (0.0)	
Race, n (%)1.060						
White	192 (72.5)	138 (61.9)	1.107	192 (72.5)	70.6 (64.1)	1.060
Black or African American	2 (0.8)	39 (17.5)		2 (0.8)	19.3 (17.6)	
Asian	31 (11.7)	7 (3.1)		31 (11.7)	3.7 (3.4)	
Other	5 (1.9)	39 (17.5)		5 (1.9)	16.4 (14.9)	
Missing	35 (13.2)	0 (0.0)		35 (13.2)	0 (0.0)	
ISS stage, n (%)						
1	92 (34.7)	33 (13.3)	0.326	92 (34.7)	39.4 (32.1)	0.073
2	109 (41.1)	42 (16.9)		109 (41.1)	57.5 (46.8)	
3	64 (24.2)	48 (19.3)		64 (24.2)	25.9 (21.1)	
4	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Missing	0 (0.0)	126 (50.6)		0 (0.0)	0 (0.0)	

Characteristic	IMROZ (IsaVRd)	Flatiron VCd (filtered)	SMD before weighting	IMROZ (IsaVRd)	Flatiron VCd weighted* (filtered)	SMD after weighting
ECOG, n (%)						
0	123 (46.4)	32 (12.9)	0.375	123 (46.4)	58.1 (47.3)	0.237
1	112 (42.3)	41 (16.5)		112 (42.3)	53.9 (43.9)	
2	29 (10.9)	22 (8.8)		29 (10.9)	10.8 (8.8)	
3	1 (0.4)	0 (0.0)		1 (0.4)	0.0 (0.0)	
Missing	0 (0.0)	154 (61.8)		0 (0.0)	0.0 (0.0)	
Cytogenetic risk, n (%)						
Standard	207 (78.1)	147 (59.0)	0.123	207 (78.1)	107.4 (87.4)	0.003
High	40 (15.1)	39 (15.7)		40 (15.1)	15.4 (12.6)	
Missing	18 (6.8)	63 (25.3)		18 (6.8)	0.0 (0.0)	
Chromosomal abnormality 1q21+, n (%)						
Present	95 (35.8)	44 (17.7)	0.032	95 (35.8)	47.0 (38.3)	0.076
Absent	152 (57.4)	66 (26.5)		152 (57.4)	75.8 (61.7)	
Missing	18 (6.8)	139 (55.8)		18 (6.8)	0.0 (0.0)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; I, Isatuximab; ISS, International Staging System; SD, standard deviation; SMD, standardised mean difference; TT, time to; TRT, treatment, VCd, bortezomib, cyclophosphamide, and dexamethasone.
Note: *The sum of patient weights are rescaled such that they equal the ESS.

Section B: Clarification on cost effectiveness data

IsaVRd vs DRd: OS and PFS extrapolations

B1. Priority question. Please carry out the following analyses:

1. **Repeat the process described in CS, Section B.3.3.1 and CS, Section B.3.3.2 to fit curves to:**
    - **IMROZ trial IsaVRd OS and PFS K-M data (first 60 months only) after DRd MAIC adjustments (i.e., data presented in CS, Figure 22 and Figure 23, up to 60 months)**
    - **MAIA trial OS and PFS K-M data for the first 60 months only**
2. **Ensure that the chosen OS and PFS curves generate estimates that fall within the upper and lower bounds of the landmark survival estimates suggested by clinical experts (CS, B.3.3.6 [Sanofi data on file, reference 136]).**
3. **Use the chosen curves to generate cost effectiveness results for IsaVRd vs DRd, including scenario analyses that use OS and PFS curves for IsaVRd and DRd that are attenuated to the lower bound, upper bound and mid-points of landmark survival estimates suggested by clinical experts.**

Answer:

Rationale for Using Full Follow-Up Data

Sanofi understands the desire to explore the influence of differential lengths of trial follow-up and limited numbers of patients at risk towards the end of trial follow-up. However, these analyses requested in B1 to B4 are counter-intuitive and do not leverage the available evidence for the following reasons:

1. **Conventional Extrapolation Techniques**: Conventional extrapolation techniques naturally apply less emphasis to the tail of the data where there are fewer patients at risk. This approach reduces the potential bias introduced by the limited number of patients in the tail.

2. **Availability of longer OS follow-up for MAIA**: The final OS analysis in MAIA with 100 months of follow-up for DRd is now available. It provides a more accurate and comprehensive source of data compared to the scenario requested by the EAG (Scenario A), which truncates the data at 60 months and which does not leverage 40 months of observed data. Scenario B where the full available follow-up for DRd captures the long-term survival trends and treatment effects more effectively, ensuring a more robust and reliable analysis. This is further explained in the section on Scenario B.

3. **Use of Clinician Estimates:** Best source of evidence is IMROZ and expert opinion should be used to inform and select the best distribution as initially done in the submission as there is no clinical experience of using IsaVRd in the UK. Additionally, the survival predictions of the selected distributions are either below or very close to the maximum estimates provided by clinicians for OS and PFS, reinforcing the validity of using the full follow-up data for all sources.

4. **Inadequacy of Censoring Data**: Censoring patients post-60 months for IsaVRd only marginally changes the survival estimates for Overall Survival (OS) and Progression-Free Survival (PFS), indicating that the tail does not introduce significant uncertainty. Additionally, censoring data after 60 months for DRd did not capture the survival trends observed in the final analysis as further explained in Scenario B in the document. Therefore, there is no reason to believe that censoring data after 60 months would better capture survival trends for IsaVRd.

5. **Consistency Across Technology Appraisals**: In the DRd TA (TA917), the entire follow-up period was utilized despite a plateau at the end of the

Kaplan-Meier curves. This approach ensures consistency and reliability in the analysis.

6. **Consideration of COVID-19 Impact**: The OS treatment effect versus DRd accounts for the 12 COVID-19-related deaths in IMROZ, which did not occur in the MAIA trial, potentially underestimating the treatment effect between IsaVRd and DRd. Considering IMROZ observed OS data up to 60 months would lower the IsaVRd survival extrapolation and would lower again the relative treatment benefit of IsaVRd vs DRd, while already conservative.

Conclusion: We recommend using the maximum available follow-up data, especially for DRd, as approximately 100 months of follow-up are now available. Extrapolations based on 60 months do not capture the full survival trends. This approach does not preclude fixing the Hazard Ratio (HR) at the end of the IMROZ follow-up, which has been done in the analyses.

Rationale for Not Attenuating Survival Curves to match clinicians estimates

1. **Reliability of IMROZ Data**: The best source of evidence is the IMROZ study. Expert opinion should be used to select the best distribution and to estimate the overall plausibility of the survival extrapolation but not to target a survival estimate at given points in time, as clinicians have no direct experience with IsaVRd. In addition, if expert opinion to be used to inform quantitatively the survival extrapolation at specific points in time rather than to check the overall plausibility of the survival extrapolations, other methods would be required rather than an attenuation factor and clinician estimates would be recommended to be collected with a different methodology (31), as highlighted by the University of Sheffield at ISPOR 2024 and which will be added to a NICE DSU Technical Support Document (TSD) on structured expert elicitation (SEE) for long-term survival outcomes to be issued shortly.

2. **Consistency with Previous Technology Appraisals**: The estimated PFS for IsaVRd from clinicians aligns with the modelled PFS for DRd in TA917, despite a statistically significant improvement in treatment effect

for IsaVRd, which increases over time. In TA917, PFS rates for DRd at 10 and 15 years using the exponential distribution were 26.3% and 13.5% whereas clinicians estimated that mean PFS for IsaVRd would be 28% and 11% at 10 and 15 years. It means that the clinicians estimates for the IsaVRd PFS may be underestimated. This may be explained by a lack of experience from clinical experts using IsaVRd in the UK so far.

3. **Robustness of PFS Extrapolations**: For PFS, all extrapolations lead to similar survival outcomes, except for the log-normal and log-logistic distributions. This consistency supports the use of the full follow-up data.

4. **Clinical Plausibility**: Attenuating the survival curves would result in an abrupt change in the hazard after the IMROZ follow-up, which is not clinically plausible especially for PFS when all extrapolations result in the same survival.

While we provide the analyses requested by the EAG, we wish to emphasise the substantial limitations of the analyses shown to answer questions B1-B4 and provide another alternative for DRd using the final OS analysis from MAIA.

The following analyses have been conducted and are presented below:

- Scenario A – Analysis requested by the EAG for: IsaVRd, DRd, Rd, VMP were right-censored at 60 months and VCd was right-censored at 84 months for OS and PFS

- Scenario B – IsaVRd ITT analysis (follow-up used in the initial submission) and DRd final OS analysis with 100 months of follow-up (updated follow-up to the original submission)

By following the previously outlined rationales, we ensure that our analysis remains both scientifically robust and clinically relevant. Scenario B, which incorporates the full follow-up data, offers a more accurate and comprehensive analysis compared to Scenario A. Consequently, Scenario B is the preferred approach and will serve as the new base-case.

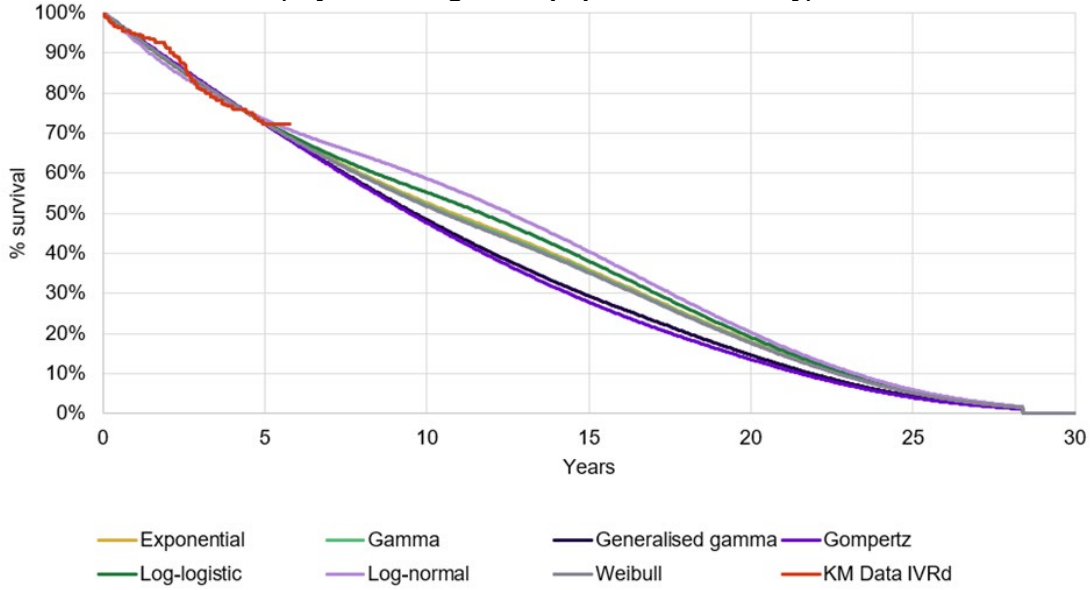
Scenario A

Overall survival extrapolation

IsaVRd

Extrapolations from IsaVRd, based on 60 months of follow-up, are presented in Figure 6. Following visual inspection, model fit statistics, and external validation, the Gompertz and Generalised gamma distributions were selected as the best distributions. Although this distribution was also chosen for the base case, it results in slightly lower long-term overall survival than when data are not censored after 60 months.

Figure 6: Overall survival IsaVRd parametric survival models informed restricted to 60 month cut off data (adjusted for general population mortality)

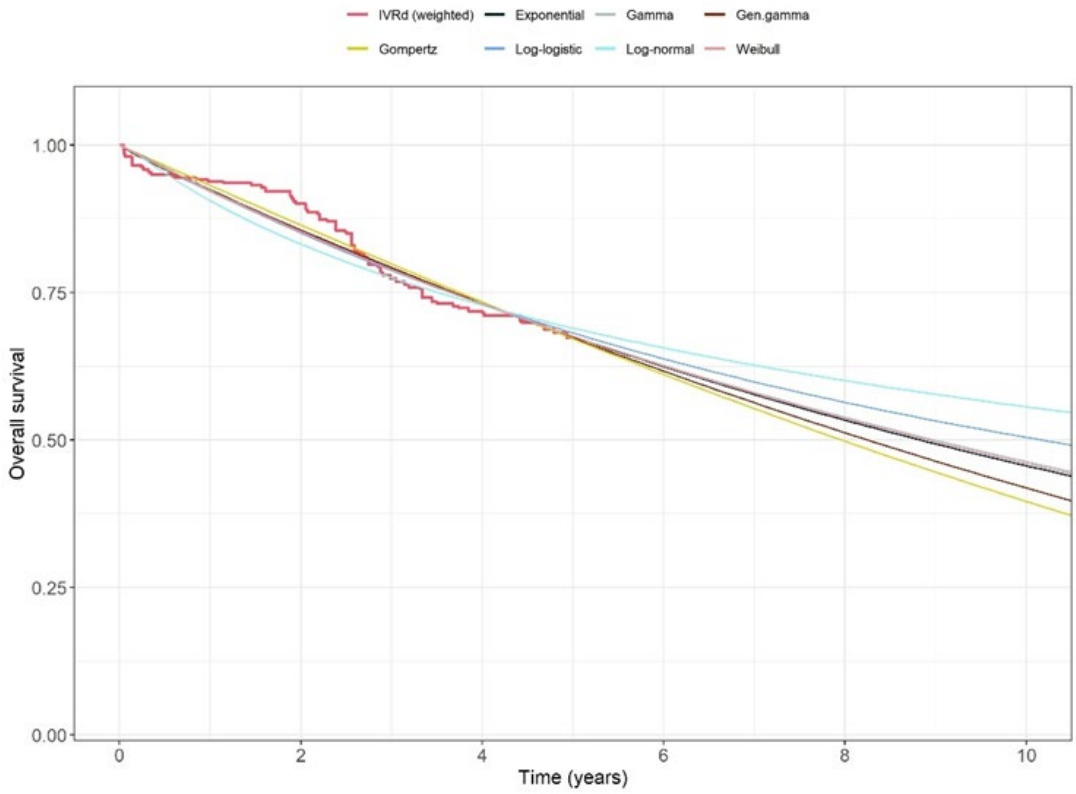


Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; KM, Kaplan–Meier.

Visual Inspection

Figure 7 shows the fit of the seven standard parametric models fit on the IMROZ follow-up. Visually, all provide a good fit over the IMROZ clinical study period except at the beginning where the survival seems to be underestimated compared to the Kaplan-Meier curve.

Figure 7: Overall survival for IsaVRd



Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; KM, Kaplan–Meier.

Model fit statistics

AIC and BIC values are provided for the standard parametric curves in Table 4. For AIC, all models, except Log-normal, are within five points of each other, indicating that there is little meaningful difference between the remaining models. For BIC, Exponential fits better than the other models. Gompertz, Weibull, Gamma and log-logistic are within six points of the best fitting model. Log-normal and generalized gamma do not fit well with more than ten points from the best fitting model. Overall, according to both AIC and BIC, the Exponential distribution fits best, followed by Gompertz, Weibull, Gamma and Log-logistic. However, selecting the exponential distribution would assume a constant HR with other comparators after adjustment with MAICs as the same distribution is used across comparators. As described in Appendix D.3, PH tests after adjustments suggest a violation of the assumption of IsaVRd versus comparators. Therefore, exponential will not be used.

Table 4: Fit statistics of overall survival extrapolation – IsaVRd

Distribution	AIC	AIC rank	AIC delta	BIC	BIC rank	BIC delta
Exponential	862	1	0	865	0	1
Gamma	864	4	2	871	6	4
Generalised gamma	865	6	4	876	11	6
Gompertz	863	2	2	870	5	2
Log-logistic	864	5	3	871	6	5
Log-normal	870	7	8	877	12	7
Weibull	864	3	2	871	6	3

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone.
Notes: AIC and BIC values are rounded to the nearest integer. Cells shaded in yellow are within five points of the best fitting model. Cells shaded in blue are within five points of the second-best-fitting model.

External validation

Table 5 shows the predicted probability of patients alive at 10, 15 and 20 years. The Gompertz and Generalised gamma distributions have the lowest survival rates, approximately 48% at 10 years, 28–29% at 15 years, and 14% at 20 years. These rates fall under the upper limits of the survival estimates collected during clinician expert interviews, which were 45% (95% CI; 35, 55) at 10 years, 24% (95% CI; 15, 33) at 15 years, and 11% at 20 years (95% CI; 5-17). The Generalised gamma and Gompertz distributions based on the unadjusted ITT Kaplan-Meier fall under the maximum values provided by the clinicians which were 60%, 35% and 20% at 10, 15 and 20 years respectively, suggesting that they also provides realistic survival rates.

Therefore, Generalised-gamma and Gompertz distributions provide the most plausible estimates for IsaVRd OS using both follow-up.

Table 5: Overall survival – proportion of patients alive at key time points for unadjusted ITT and 60 month restricted (adjusted for general population mortality)

	10 years		15 years		20 years	
Distribution	Unadjusted ITT	60 months adjusted	Unadjusted ITT	60 months adjusted	Unadjusted ITT	60 months adjusted
Exponential	53.53%	55.17%	36.72%	35.82%	18.38%	17.93%
Gamma	53.55%	52.07%	36.84%	35.38%	18.39%	17.71%
Generalised gamma	51.70%	48.33%	34.50%	29.26%	17.30%	14.56%
Gompertz	52.36%	47.56%	35.40%	27.71%	17.74%	13.48%
Log-logistic	56.30%	55.17%	38.97%	37.95%	19.48%	19.00%
Log-normal	59.22%	58.61%	41.01%	40.31%	20.49%	20.18%
Weibull	53.42%	51.72%	36.62%	35.02%	18.33%	17.53%
Clinicians estimates %, (95%CI)	45% (35-55) Max: 60%		24% (15-33) Max: 35%		11% (5-17) Max: 20%	

Abbreviations: CI, confidence interval; ITT, intention to treat.

Comparators not included in IMROZ

Time-varying HRs and model selection

In the absence of head-to-head clinical trials between IsaVRd and comparators of interest, MAICs and IPW were conducted. PH assumption was tested between IsaVRd and comparators after matching. Diagnostic tests indicate that PH does not hold between IsaVRd and all other comparators. Full details are presented in Appendix I.5. Therefore, an approach that relaxes the PH assumption is preferred and used in the base-case.

For implementation in the cost-effectiveness model, the time-varying HRs from ITCs were anchored to the IsaVRd curve selected from fitting parametric survival models to the IMROZ ITT data. According to NICE DSU TSD 14, it is recommended to use the same distribution across comparators. Additionally, although the survival of IsaVRd may change when matching to the comparator population in the MAICs, there is no obvious reason to think the survival for IsaVRd would follow a different distribution with different comparators. Therefore, the same distribution was used to estimate time-varying HR after matching and for the IsaVRd distribution in the model.

Time-varying HRs for IsaVRd versus comparators are presented in the following tables. Values which are less than 1 suggest a survival benefit for IsaVRd compared to the comparators.

Given that all distributions suggest an improving treatment effect versus DRd except the Gompertz which has very wide confidence intervals, the Generalised gamma distribution is used as the base-case for this scenario to better reflect the

overall trend across all distributions. Generalised gamma was also the committee's preferred distribution to extrapolate DRd in TA917. The Generalised-Gamma was also considered a realistic distribution to model IsaVRd as it provided the lowest survival with the Gompertz for IsaVRd when data are right-censored after 60 months.

Additionally, all distributions over-estimate the DRd survival against the published final MAIA OS analysis, biasing the comparison versus IsaVRd in this scenario as further explained in Scenario B.

Table 6: Landmark HRs for overall survival – IsaVRd versus DRd

Time (year)	HR (95% CI) for IsaVRd versus DRd						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.67*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; DRd, daratumumab, lenalidomide, and dexamethasone; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone.
* End of IMROZ follow-up.

Table 7: Landmark HRs for overall survival – IsaVRd versus Rd

Time (year)	HR (95% CI) for IsaVRd versus Rd						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.67*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone.
* End of IMROZ follow-up.

Table 8: Landmark HRs for overall survival – IsaVRd versus VMP

Time (year)	HR (95% CI) for IsaVRd versus VMP						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
1	0.52 (0.37, 0.73)	0.55 (0.38, 0.78)	0.60 (0.38, 0.84)	0.69 (0.44, 1.06)	0.57 (0.37, 0.82)	0.54 (0.37, 0.76)	0.58 (0.39, 0.83)
2	0.52 (0.37, 0.73)	0.49 (0.35, 0.71)	0.51 (0.37, 0.72)	0.55 (0.40, 0.78)	0.49 (0.35, 0.71)	0.51 (0.36, 0.74)	0.50 (0.36, 0.71)
5	0.52 (0.37, 0.73)	0.44 (0.29, 0.72)	0.36 (0.22, 0.70)	0.29 (0.14, 0.61)	0.47 (0.31, 0.76)	0.50 (0.34, 0.79)	0.41 (0.26, 0.70)
5.67*	0.52 (0.37, 0.73)	0.43 (0.28, 0.73)	0.33 (0.19, 0.71)	0.25 (0.10, 0.61)	0.48 (0.31, 0.78)	0.50 (0.34, 0.80)	0.39 (0.24, 0.70)
10	0.52 (0.37, 0.73)	0.41 (0.24, 0.75)	0.20 (0.02, 0.74)	0.10 (0.01, 0.64)	0.52 (0.33, 0.87)	0.50 (0.33, 0.82)	0.35 (0.19, 0.74)
28	0.52 (0.37, 0.73)	0.39 (0.21, 0.78)	0.07 (0.00, 1.00)	0.00 (0.00, 0.91)	0.63 (0.41, 0.99)	0.51 (0.32, 0.87)	0.28 (0.11, 0.81)

Abbreviations: CI, confidence interval; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone.
* End of IMROZ follow-up.

Table 9: Landmark HRs for overall survival – IsaVRd vs VCd

Time (year)	HR (95% CI) for IsaVRd versus VCd						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
1	0.47 (0.33, 0.66)	0.48 (0.33, 0.70)	0.48 (0.33, 0.73)	0.46 (0.29, 0.73)	0.45 (0.30, 0.69)	0.45 (0.31, 0.67)	0.48 (0.32, 0.72)
2	0.47 (0.33, 0.66)	0.46 (0.32, 0.65)	0.47 (0.34, 0.69)	0.47 (0.32, 0.68)	0.43 (0.29, 0.63)	0.43 (0.30, 0.62)	0.46 (0.33, 0.67)
5	0.47 (0.33, 0.66)	0.44 (0.28, 0.69)	0.44 (0.28, 0.77)	0.50 (0.27, 0.97)	0.46 (0.30, 0.73)	0.42 (0.27, 0.65)	0.44 (0.27, 0.73)
5.67*	0.47 (0.33, 0.66)	0.44 (0.27, 0.70)	0.44 (0.27, 0.79)	0.51 (0.24, 1.12)	0.47 (0.30, 0.76)	0.42 (0.27, 0.65)	0.44 (0.27, 0.75)
10	0.47 (0.33, 0.66)	0.43 (0.25, 0.74)	0.43 (0.22, 0.92)	0.56 (0.11, 2.96)	0.54 (0.34, 0.89)	0.42 (0.27, 0.68)	0.43 (0.22, 0.85)
20	0.47 (0.33, 0.66)	0.42 (0.23, 0.79)	0.41 (0.15, 1.22)	0.69 (0.02, 31.45)	0.63 (0.40, 1.02)	0.43 (0.26, 0.71)	0.41 (0.18, 1.01)
28	0.47 (0.33, 0.66)	0.42 (0.22, 0.81)	0.41 (0.12, 1.49)	0.83 (0.00, 210.79)	0.68 (0.43, 1.07)	0.43 (0.26, 0.73)	0.41 (0.15, 1.10)

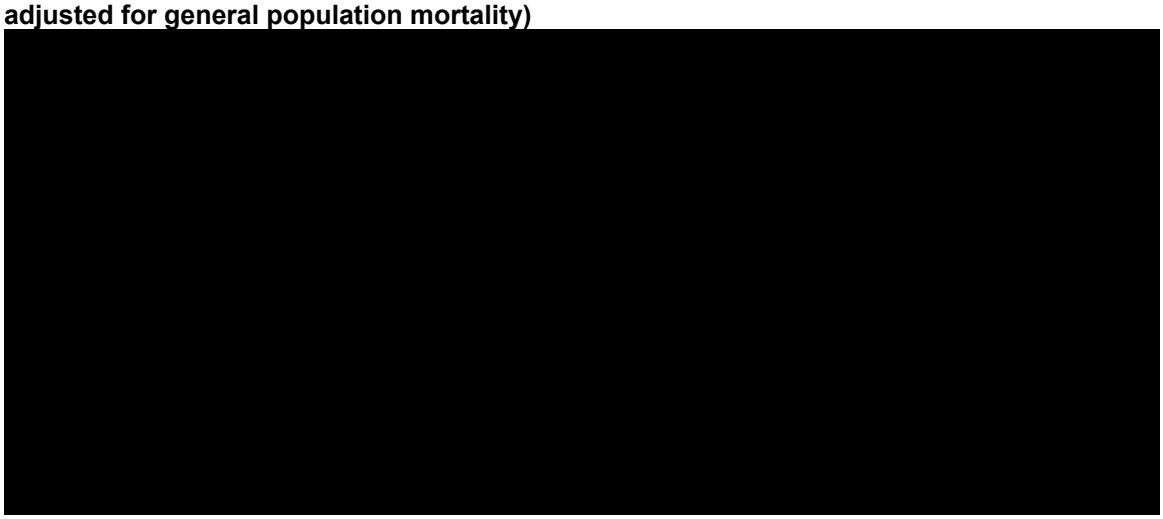
Abbreviations: CI, confidence interval; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone.
* End of IMROZ follow-up.

Fixed treatment effect from the end of IMROZ trial follow-up for OS

The HRs of IsaVRd versus all comparators were fixed at the end of the IMROZ follow-up (5.67 years) and for the remainder of the model time horizon due to an improving relative treatment effect for OS of IsaVRd compared with all comparators. According to the NICE TA917, the Committee agreed that the HR should be fixed from the end of the follow-up period to adopt a conservative approach considering the improving HR over time and the absence of longer-term data.

Final overall survival using the generalised gamma distribution for IsaVRd and all comparators is presented in Figure 8.

Figure 8: Overall survival for IsaVRd, DRd, Rd, VMP, and VCd (lifetime time horizon – adjusted for general population mortality)



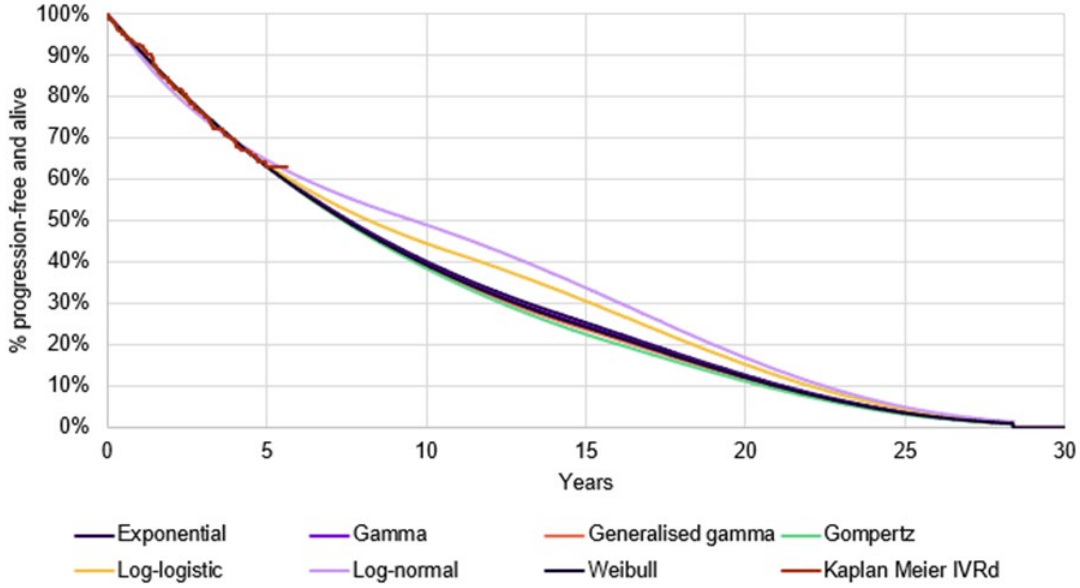
Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; KM, Kaplan-Meier; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; Rd, lenalidomide and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

Progression-free survival extrapolation

IsaVRd

Extrapolations from IsaVRd, based on 60 months of follow-up, are presented in Figure 9. Following visual inspection, model fit statistics, and external validation, Weibull was selected as the best distribution. It results in slightly lower long-term PFS than when data are not censored after 60 months.

Figure 9: Progression-free survival IsaVRd parametric survival models informed restricted to 60 month cut off data (adjusted for general population mortality)

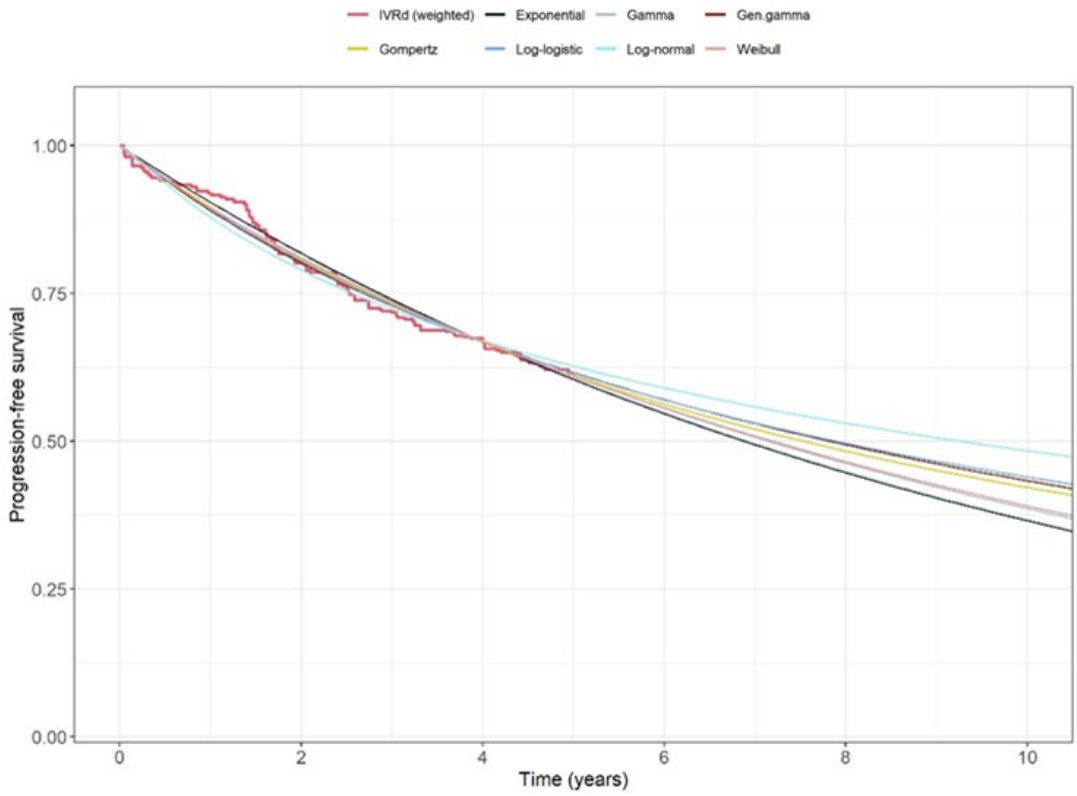


Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; KM, Kaplan–Meier.

Visual Inspection

Figure 10 shows the fit of the seven standard parametric models fit on the IMROZ follow-up. Visually, all provide a good fit over the IMROZ clinical study period except at the beginning where extrapolations tend to underestimate the Kaplan-Meier.

Figure 10: Progression-free survival for IsaVRd



Abbreviations: IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone; KM, Kaplan–Meier.

Model fit statistics

AIC and BIC values are provided for the standard parametric curves in Table 10. For AIC, all models, except Log-normal, are within five points of each other, indicating that there is little meaningful difference between the remaining models regarding the goodness of fit to the observed data. For BIC, Exponential fits better than the other models. Weibull, Gamma, Gompertz and log-logistic are within six points of the best fitting model. Log-normal and generalised gamma do not fit well with more than ten points from the best fitting model. Overall, according to both AIC and BIC, the Exponential distribution fits best, followed by Weibull, Gamma, Gompertz and Log-logistic. However, selecting the exponential distribution would assume a constant HR with other comparators after adjustment with MAICs as the same distribution is used across comparators. As described in Appendix D.3, PH tests after adjustments suggest a violation of the assumption of IsaVRd versus comparators. Therefore, the exponential distribution will not be used.

Table 10: Fit statistics of progression-free survival extrapolation – IsaVRd

Distribution	AIC	AIC rank	AIC delta	BIC	BIC rank	BIC delta
Exponential	990	1	0	994	1	0
Gamma	992	3	2	999	3	6
Generalised gamma	994	6	4	1005	7	11
Gompertz	992	4	2	999	4	6
Log-logistic	992	5	2	1000	5	6
Log-normal	996	7	6	1003	6	10
Weibull	992	2	2	999	2	6

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; IsaVRd, isatuximab, bortezomib, lenalidomide and dexamethasone.
Notes: AIC and BIC values are rounded to the nearest integer. Cells shaded in yellow are within five points of the best fitting model. Cells shaded in blue are within five points of the second-best-fitting model.

External validation

Table 11 shows that the log-normal and log-logistic models have the highest survival probability at later time points, with 30 to 31% of patients alive and PF at 15 years. The Weibull, Gamma, Gompertz distributions have the lowest and similar survival rates, approximately 40% at 10 years, 23-24% at 15 years, and 11-12% at 20 years. These rates are higher than the upper limits of the survival estimates collected during clinician expert interviews, which were 28% (95% CI; 23, 33) at 10 years, 11% (95% CI; 2, 16) at 15 years, and 2% (95% CI; 0, 6) at 20 years. However, they are aligned or slightly higher than the maximum survival rates provided by clinicians, which were 40% at 10 years, 20% at 15 years and 10% at 20 years.

The range of estimates indicates that some clinicians may consider the longer-term extrapolation of the model to be realistic. Therefore, Gamma, Weibull and Gompertz and distributions provide the most plausible estimates for IsaVRd PFS. Weibull was chosen in the base case due to a better fit statistic (Table 11).

Table 11: Progression-free survival – proportion of patients progression-free at key time points for unadjusted ITT and 60 month restricted (adjusted for general population mortality)

	10 years		15 years		20 years	
Distribution	Unadjusted ITT	60 months adjusted	Unadjusted ITT	60 months adjusted	Unadjusted ITT	60 months adjusted
Exponential	40.60%	40.25%	25.67%	24.37%	17.61%	12.12%
Gamma	40.20%	39.60%	25.19%	23.92%	12.61%	11.90%
Generalised gamma	40.79%	39.11%	26.09%	23.47%	13.06%	11.68%
Gompertz	40.62%	38.59%	25.69%	22.58%	12.86%	11.23%
Log-logistic	44.71%	42.36%	30.12%	25.65%	15.08%	12.76%
Log-normal	46.39%	42.15%	31.25%	26.13%	15.65%	13.00%
Weibull	40.15%	39.44%	25.10%	23.78%	12.57%	11.83%
Clinicians' estimates %, (95%CI)	28% (23-33) Max 40%		11% (2-16) Max 20%		2% (0-6) Max 10%	

Abbreviations: CI, confidence interval; ITT, intention to treat

Comparators not included in IMROZ

Time-varying HRs and model selection

PH assumption was tested between IsaVRd and comparators after matching. Diagnostic tests indicate that PH does not hold between IsaVRd and all other comparators. Full details are presented in Appendix I.5. Therefore, an approach that relaxes the PH assumption is preferred and used in the base-case. Constant HR MAICs and IPW will be tested in a scenario analysis.

In line with overall survival, the same distribution was used to estimate time-varying HR after matching and for the IsaVRd distribution in the model. Time-varying HRs for IsaVRd versus comparators are presented in the following tables. Values which are less than 1 suggest a survival benefit for IsaVRd compared to the comparators.

All distributions suggest an improving treatment effect versus DRd except the log-logistic. However, this distribution has been excluded because it generates one of the highest survival among the distributions for IsaVRd. The Weibull distribution will be used as the base-case for due to fit statistics. The Gamma could be used in alignment with the original submission, however, survival for IsaVRd and HRs versus DRd are the same as for the Weibull and no impact is expected from using this distribution.

Table 12: Landmark HRs for progression-free survival – IsaVRd versus DRd

Time (year)	HR (95% CI) for IsaVRd versus DRd						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.67*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; DRd, daratumumab, lenalidomide, and dexamethasone; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone.
* End of IMROZ follow-up.

Table 13: Landmark HRs for progression-free survival – IsaVRd versus Rd

Time (year)	HR (95% CI) for IsaVRd versus Rd						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.67*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone.
* End of IMROZ follow-up.

Table 14: Landmark HRs for progression-free survival – IsaVRd versus VMP

Time (year)	HR (95% CI) for IsaVRd versus VMP						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
1	0.43 (0.32, 0.58)	0.44 (0.33, 0.60)	0.44 (0.32, 0.60)	0.47 (0.32, 0.67)	0.41 (0.30, 0.57)	0.43 (0.31, 0.59)	0.45 (0.33, 0.61)
2	0.43 (0.32, 0.58)	0.41 (0.30, 0.57)	0.41 (0.30, 0.58)	0.43 (0.32, 0.58)	0.40 (0.29, 0.56)	0.41 (0.30, 0.58)	0.41 (0.30, 0.57)
5	0.43 (0.32, 0.58)	0.37 (0.25, 0.58)	0.37 (0.25, 0.59)	0.35 (0.17, 0.72)	0.45 (0.31, 0.68)	0.41 (0.28, 0.60)	0.36 (0.24, 0.60)
5.67*	0.43 (0.32, 0.58)	0.37 (0.25, 0.58)	0.37 (0.24, 0.60)	0.33 (0.14, 0.79)	0.46 (0.32, 0.70)	0.41 (0.28, 0.60)	0.36 (0.23, 0.61)
10	0.43 (0.32, 0.58)	0.35 (0.23, 0.59)	0.35 (0.21, 0.63)	0.24 (0.04, 1.43)	0.53 (0.36, 0.80)	0.41 (0.28, 0.62)	0.33 (0.19, 0.65)
28	0.43 (0.32, 0.58)	0.34 (0.21, 0.61)	0.34 (0.17, 0.66)	0.12 (0.00, 6.03)	0.62 (0.42, 0.90)	0.42 (0.27, 0.64)	0.30 (0.15, 0.70)

Abbreviations: CI, confidence interval; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; VMP, bortezomib, melphalan, and prednisone.
* End of IMROZ follow-up.

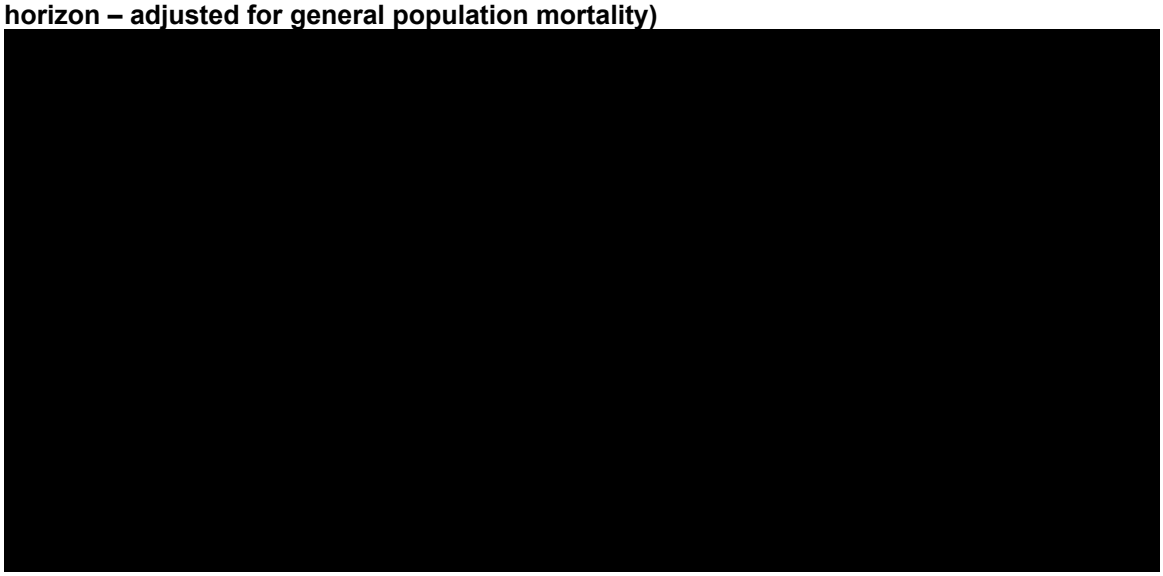
Table 15: Landmark HRs for progression-free survival – IsaVRd vs VCd

Time (year)	HR (95% CI) for IsaVRd versus VCd						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
1	0.35 (0.26, 0.46)	0.35 (0.25, 0.47)	0.34 (0.24, 0.47)	0.33 (0.23, 0.48)	0.30 (0.21, 0.43)	0.33 (0.24, 0.45)	0.35 (0.25, 0.49)
2	0.35 (0.26, 0.46)	0.33 (0.24, 0.46)	0.33 (0.24, 0.47)	0.34 (0.25, 0.47)	0.31 (0.22, 0.43)	0.32 (0.23, 0.44)	0.34 (0.25, 0.47)
5	0.35 (0.26, 0.46)	0.32 (0.21, 0.49)	0.32 (0.21, 0.51)	0.39 (0.20, 0.75)	0.39 (0.27, 0.58)	0.33 (0.23, 0.48)	0.33 (0.21, 0.53)
5.67*	0.35 (0.26, 0.46)	0.32 (0.21, 0.49)	0.32 (0.21, 0.52)	0.40 (0.18, 0.87)	0.41 (0.28, 0.61)	0.33 (0.23, 0.49)	0.33 (0.20, 0.54)
10	0.35 (0.26, 0.46)	0.32 (0.20, 0.52)	0.33 (0.20, 0.55)	0.47 (0.10, 2.39)	0.50 (0.34, 0.74)	0.34 (0.23, 0.51)	0.32 (0.18, 0.60)
20	0.35 (0.26, 0.46)	0.31 (0.19, 0.54)	0.33 (0.18, 0.59)	0.70 (0.02, 24.65)	0.61 (0.42, 0.87)	0.35 (0.23, 0.54)	0.31 (0.14, 0.70)
28	0.35 (0.26, 0.46)	0.31 (0.18, 0.55)	0.33 (0.17, 0.62)	0.96 (0.01, 162.46)	0.65 (0.46, 0.92)	0.36 (0.23, 0.56)	0.31 (0.13, 0.76)

Abbreviations: CI, confidence interval; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone.
* End of IMROZ follow-up.

Final progression-free survival using the Weibull distribution for IsaVRd and all comparators is presented in Figure 8. Treatment effect was not fixed at the end of the follow-up for PFS, in alignment with the DRd TA (TA917).

Figure 11: Progression-free survival for IsaVRd, DRd, Rd, VMP, and VCd (lifetime time horizon – adjusted for general population mortality)

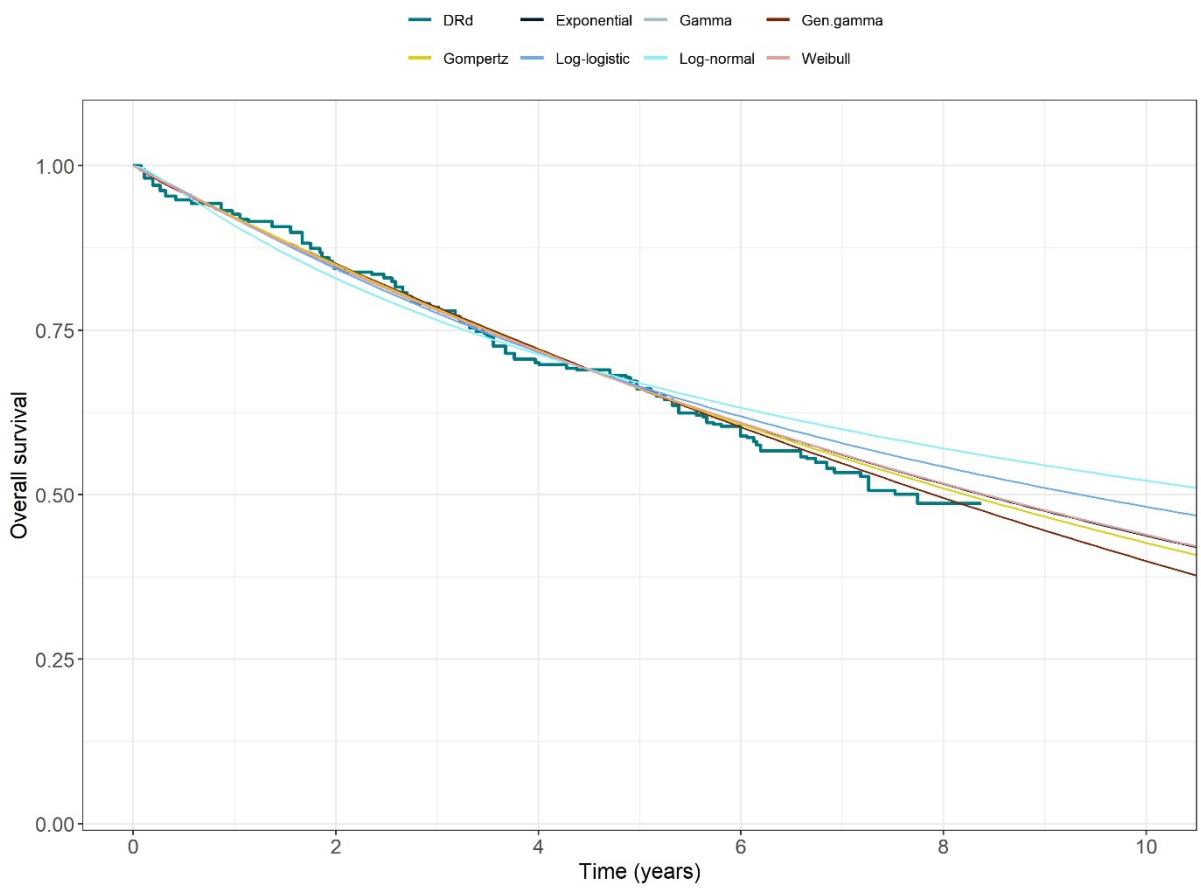


Scenario B

This scenario has been conducted due to the availability of the final OS analysis from the MAIA clinical trial, published after the last update of the clinical SLR. In this final analysis, DRd and Rd now have approximately 100 months of OS follow-up, representing 40 additional months compared to the analysis requested by the EAG where data are right-censored at 60 months. This follow-up better reflects the long-term extrapolation of DRd and Rd. This additional data-cut is only available for OS.

Parametric distributions were fitted to the DRd OS truncated at 60 months and overlaid on the KM with 100 months of follow-up in Figure 12. The conclusion is that extrapolations based on the 60-months follow-up data fail to predict the subsequently observed data and tend to overestimate the OS.

Figure 12: Overall survival DRd – parametric distributions fitted to the DRd truncated data at 60 months with the longer term data overlaid



Abbreviations: DRd, daratumumab lenalidomide and dexamethasone

Given that censoring patients after 60 months for DRd failed to capture the longer-term OS, this scenario will also use the longest available follow-up for IsaVRd.

In line with the base-case in the original submission, PH assumption was tested between IsaVRd and comparators after matching. Diagnostic tests indicate that PH does not hold between IsaVRd and all other comparators. Full details are presented in Appendix I.5. Therefore, an approach that relaxes the PH assumption is preferred and used in the base-case.

The same distribution was used to estimate time-varying HR after matching and for the IsaVRd distribution in the model. Time-varying HRs for IsaVRd versus comparators are presented in the following tables. Values which are less than 1 suggest a survival benefit for IsaVRd compared to the comparators.

All distributions indicate an improving treatment effect compared to DRd. The generalised gamma distribution will be used as the base-case, in alignment with the committee's preferred assumption in DRd TA (TA917). The generalised gamma distribution also provides the lowest survival rates, along with the

Gompertz distribution. Although the Gompertz distribution could have been used, it produces unrealistic results for the comparison with Rd, as the HR fluctuates and becomes closer to 1 than with DRd. This would imply that the hazard of death for DRd is higher than for Rd at some point, which is not consistent with TA917. Additionally, the Gompertz distribution shows much larger confidence intervals, highlighting the uncertainty associated with this distribution for Rd. However, the results are not sensitive between these two distributions when comparing with DRd.

Table 16: Landmark HRs for overall survival – IsaVRd versus DRd

Time (year)	HR (95% CI) for IsaVRd versus DRd						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.67*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* End of IMROZ follow-up

Table 17: Landmark HRs for overall survival – IsaVRd versus Rd

Time (year)	HR (95% CI) for IsaVRd versus Rd						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.67*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* End of IMROZ follow-up

Figure 13 presents the final overall survival using the generalised gamma distribution for IsaVRd and all comparators. The analysis used the full follow-up data available from all sources, including the final OS analysis for DRd. The treatment effect was fixed at the end of the IMROZ follow-up, in alignment with the DRd TA (TA917).

Figure 13: Overall survival for IsaVRd, DRd, Rd, VMP, and VCd (lifetime time horizon – adjusted for general population mortality)

Question 3. Base case results for pairwise comparison IsaVRd vs DRd for Scenario A and Scenario B are presented in Table 24 and Table 24 using the list and PAS prices (PAS applied to only isatuximab), respectively.

Table 18: Base-case deterministic results at list price (IsaVRd vs DRd)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Scenario A							
DRd	[redacted]	10.506	[redacted]	-	-	-	
IsaVRd	[redacted]	10.825	[redacted]	[redacted]	0.319	[redacted]	IsaVRd dominates
Scenario B							
DRd	[redacted]	10.721	[redacted]	-	-	-	-
IsaVRd	[redacted]	11.441	[redacted]	[redacted]	0.720	[redacted]	IsaVRd dominates

Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; ICER, incremental cost-effectiveness ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years

Table 19: Base-case deterministic results at PAS price (IsaVRd vs DRd)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Scenario A							
DRd	[redacted]	10.506	[redacted]	-	-	-	-
IsaVRd	[redacted]	10.825	[redacted]	[redacted]	0.319	[redacted]	[redacted]
Scenario B							
DRd	[redacted]	10.721	[redacted]	-	-	-	-
IsaVRd	[redacted]	11.441	[redacted]	[redacted]	0.720	[redacted]	[redacted]

Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; ICER, incremental cost-effectiveness ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years

Isatuximab PAS,[redacted]

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IsaVRd vs Rd: OS and PFS extrapolation

B2. Priority question. Please carry out the following analyses:

1. **Repeat the process described in CS, Section B.3.3.1 and Section B.3.3.2 to fit curves to:**
   - **IMROZ trial IsaVRd OS and PFS K-M data (first 60 months only) after Rd MAIC adjustments (i.e. data presented in CS, Figure 25 and Figure 26, up to 60 months)**
   - **MAIA trial OS and PFS K-M data for the first 60 months only**
2. **Ensure that the chosen OS and PFS curves generate estimates that fall within the upper and lower bounds of the landmark survival estimates suggested by clinical experts (CS, B.3.3.6 [Sanofi data on file, reference 136]).**
3. **Use the chosen curves to generate cost effectiveness results for IsaVRd vs Rd, including scenario analyses that use OS and PFS curves for IsaVRd and Rd that are attenuated to the lower bound, upper bound and mid-points of landmark survival estimates suggested by clinical experts.**

Answer: Questions 1 & 2. Please refer to the answer in Section B1.

Question 3. Base case results for pairwise comparison IsaVRd vs Rd for Scenario A and Scenario B are presented in Table 20 and Table 21 using the list and PAS prices (PAS applied to only isatuximab), respectively.

Table 20: Base-case deterministic results at list price (IsaVRd vs Rd)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Scenario A							
Rd	[redacted]	7.752	[redacted]	-	-	-	-
IsaVRd	[redacted]	10.825	[redacted]	[redacted]	3.073	[redacted]	£176,449
Scenario B							
Rd	[redacted]	8.685	[redacted]	-	-	-	-
IsaVRd	[redacted]	11.441	[redacted]	[redacted]	2.755	[redacted]	£178,058

Abbreviations: Rd, lenalidomide, and dexamethasone; ICER, incremental cost-effectiveness ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years

Table 21: Base-case deterministic results at PAS price (IsaVRd vs Rd)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Scenario A							
Rd	[redacted]	7.752	[redacted]				
IsaVRd	[redacted]	10.825	[redacted]	[redacted]	3.073	[redacted]	[redacted]
Scenario B							
Rd	[redacted]	8.685	[redacted]				
IsaVRd	[redacted]	11.441	[redacted]	[redacted]	2.755	[redacted]	[redacted]

Abbreviations: Rd, lenalidomide, and dexamethasone; ICER, incremental cost-effectiveness ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years

Isatuximab PAS, [redacted]

IsaVRd vs VMP: OS and PFS extrapolations

B3. Priority question. Please carry out the following analyses:

1. **Repeat the process described in CS, Section B.3.3.1 and Section B.3.3.2 to fit curves to:**
   - **IMROZ trial IsaVRd OS and PFS K-M data (first 60 months only) after VMP MAIC adjustments (i.e. data presented in CS, Figure 27 and Figure 28, up to 60 months)**
   - **ALCYONE trial OS and PFS K-M data for the first 60 months only**
2. **Ensure that the chosen OS and PFS curves generate estimates that fall within the upper and lower bounds of the landmark survival estimates suggested by clinical experts (CS, B.3.3.6 [Sanofi data on file, reference 136]).**
3. **Use the chosen curves to generate cost effectiveness results for IsaVRd vs VMP, including scenario analyses that use OS and PFS curves for IsaVRd and VMP that are attenuated to the lower bound, upper bound and mid-points of landmark survival estimates suggested by clinical experts.**

Answer:

Questions 1 & 2. Please refer to the answer in Section B1.

Question 3. Base case results for pairwise comparison IsaVRd vs VMP for Scenario A and Scenario B are presented in Table 22 and Table 23 using the list and PAS prices (PAS applied to only isatuximab), respectively.

Table 22: Base-case deterministic results at list price (IsaVRd vs VMP)

Techno-logies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Scenario A							
VMP	[redacted]	5.794	[redacted]				
IsaVRd	[redacted]	10.825	[redacted]	[redacted]	5.031	[redacted]	£101,171
Scenario B							
VMP	[redacted]	6.204	[redacted]				
IsaVRd	[redacted]	11.441	[redacted]	[redacted]	5.237	[redacted]	£99,329

Abbreviations: VMP, bortezomib, melphalan and prednisolone; ICER, incremental cost-effectiveness ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years

Table 23: Base-case deterministic results at PAS price (IsaVRd vs VMP)

Techno-logies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Scenario A							
VMP	[redacted]	5.794	[redacted]				
IsaVRd	[redacted]	10.825	[redacted]	[redacted]	5.031	[redacted]	[redacted]
Scenario B							
VMP	[redacted]	6.204	[redacted]				
IsaVRd	[redacted]	11.441	[redacted]	[redacted]	5.237	[redacted]	[redacted]

Abbreviations: VMP, bortezomib, melphalan and prednisolone; ICER, incremental cost-effectiveness ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years

Isatuximab PAS, [redacted]

IsaVRd vs VCd: OS and PFS extrapolations

B4. Priority question. Please carry out the following analyses:

1. **Repeat the process described in CS, Section B.3.3.1 and Section B.3.3.2 to fit curves to:**
   - **IMROZ trial IsaVRd OS and PFS K-M data (first 60 months only) (i.e. data presented in CS, Figure 29 and Figure 30, up to 60 months)**
   - **Flatiron VCd OS and PFS K-M data, weighted using IMROZ trial IsaVRd data, for the first 84 months (CS, Figures 29 and 30)**
2. **Ensure that the chosen OS and PFS curves generate estimates that fall within the upper and lower bounds of the landmark survival estimates suggested by clinical experts (CS, B.3.3.6 [Sanofi data on file, reference 136]).**
3. **Use the chosen curves to generate cost effectiveness results for IsaVRd vs VCd, including scenario analyses that use OS and PFS curves for IsaVRd and VCd that are attenuated to the lower bound, upper bound and mid-points of landmark survival estimates suggested by clinical experts.**

Answer:

Questions 1 & 2. Please refer to the answer in Section B1.

Question 3. Base case results for pairwise comparison IsaVRd vs VCd for Scenario A and Scenario B are presented in Table 24 and Table 25 using the list and PAS prices (PAS applied to only isatuximab), respectively.

Table 24: Base-case deterministic results at list price (IsaVRd vs VCd)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Scenario A							
VCd	[redacted]	6.154	[redacted]				
IsaVRd	[redacted]	10.825	[redacted]	[redacted]	4.671	[redacted]	£126,328
Scenario B							
VCd	[redacted]	6.674	[redacted]	-	-	-	-
IsaVRd	[redacted]	11.441	[redacted]	[redacted]	4.767	[redacted]	£129,975

Abbreviations: VCd, bortezomib, cyclophosphamide, and dexamethasone; ICER, incremental cost-effectiveness ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years

Table 25: Base-case deterministic results at PAS price (IsaVRd vs VCd)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Scenario A							
VCd	[redacted]	6.154	[redacted]				
IsaVRd	[redacted]	10.825	[redacted]	[redacted]	4.671	[redacted]	[redacted]
Scenario B							
VCd	[redacted]	6.674	[redacted]				
IsaVRd	[redacted]	11.441	[redacted]	[redacted]	4.767	[redacted]	[redacted]

Abbreviations: VCd, bortezomib, cyclophosphamide, and dexamethasone; ICER, incremental cost-effectiveness ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years

Isatuximab PAS, [redacted]

B5. Priority question. For each comparator, please generate the results presented in CS, Table 72 using MAIC adjusted IMROZ trial IsaVRd data.

Answer: We believe there is a typo in the request, and that Table 82, which contains ICERs versus DRd at PAS price, is requested instead of Table 72. If the request was indeed for Table 72, the values calculated are expressed as the rate of patients with a subsequent treatment among those who experienced a Progression-Free Survival (PFS) event. This method ensures that comparing values between trials with different follow-up periods does not introduce bias, as the rates are standardised per PFS event. Therefore, the values can be compared even if derived based on clinical trials with different follow-up. Additionally, the data used to derive the proportion of patients with a subsequent treatment among those with a PFS event for IMROZ and MAIA are based on similar median follow-up of 59.7months and 56.2 months respectively.

ICERs versus each comparator at PAS price presented below.

Table 26. Base-case deterministic results at PAS price for isatuximab (Table 82 in Submission)

Technologies	Total			Incremental pairwise IsaVRd vs comparator			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Scenario A							
IsaVRd	[redacted]	10.825	[redacted]				
DRd	[redacted]	10.721	[redacted]	[redacted]	0.319	[redacted]	[redacted]
Rd	[redacted]	7.752	[redacted]	[redacted]	3.073	[redacted]	[redacted]
VMP	[redacted]	5.794	[redacted]	[redacted]	5.031	[redacted]	[redacted]
VCd	[redacted]	6.154	[redacted]	[redacted]	4.671	[redacted]	[redacted]
Scenario B							
IsaVRd	[redacted]	11.441	[redacted]				
DRd	[redacted]	10.721	[redacted]	[redacted]	0.720	[redacted]	[redacted]
Rd	[redacted]	8.685	[redacted]	[redacted]	2.755	[redacted]	[redacted]
VMP	[redacted]	6.204	[redacted]	[redacted]	5.237	[redacted]	[redacted]
VCd	[redacted]	6.674	[redacted]	[redacted]	4.767	[redacted]	[redacted]

Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; Rd, daratumumab, lenalidomide, and dexamethasone; VMP, bortezomib, melphalan and prednisolone; VCd, bortezomib, cyclophosphamide, and dexamethasone; ICER, incremental cost-effectiveness ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and

dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years

Isatuximab PAS, [redacted]

Companion intervention and comparator prices

B6. Please see the below issues with the eMIT and BNF prices listed in table 108 of Appendix I and used in the model. Please provide an updated table 108 within your clarification response with any amendments made, as requested below:

1. **The eMIT prices used in the company submission are not using the most recent eMIT prices from October 2024. Whilst it is acknowledged that this was only released a short time before the company provided its evidence submission, there are some substantial differences, particularly for lenalidomide. Please update all eMIT prices used in the model and listed within the company submission with the most recent eMIT prices available from October 2024.**
2. **Please check and correct the following in table 108:**
    a. **The table reports that the dosage for dexamethasone (DFN046) as 6.6mg/1ml, but the eMIT database reports this as 6.6mg/2ml.**
    b. **There appear to be a number of errors with prednisolone listed within the table:**
        i. **All formulations of prednisolone (DFC024, DFC008, etc) reproduced from the eMIT database and BNF are incorrectly listed as prednisone**
        ii. **There appears to be misordering of the BNF sourced tariffs. Please check and correct these.**
        iii. **Some of the tablet sizes are incorrect (prednisolone 10 and 30 mg are listed as 39 and 30 tablet packs instead of 28). Please check and correct these.**

iv. **DFN050 refers to 'Prednisolone 10mg/ml oral solution sugar free / Packsize 1' in the eMIT database. There is no eMIT or BNF price for 300 mg or 30 mL oral solution bottle (50mg/5ml) as listed in the table. Please check and correct this.**

Answer: Sanofi has reviewed and updated Table 108 in Appendix I to address the issues raised by EAG (Table 27). All changes reflect the most recent eMIT prices from October 2024, and corrections have been made to align with the accurate listings in the eMIT, BNF, and MIMS databases. Additionally, we provide Table 109 in Appendix I to further update the subsequent treatment drug costs in the submission (Table 28) and Table 68 in Document B to reflect updated concomitant treatment list prices (Table **29**).

Table 27: List prices of intervention and comparator drugs (Table 108 in CS, Appendix I)

Treatment	Pack size	Form	Quantity per unit (mg)	Cost per pack (£)	Source (pack cost)
Isatuximab (Isa) IV	1	5.0 ml (vial)	100mg/5ml	506.94	BNF 2025 - medicinal forms
Isatuximab (Isa) IV	1	25.0 ml (vial)	500mg/25ml	2,534.69	BNF 2025 - medicinal forms
Bortezomib (V)	1	Powder for solution for injection vials	1	217.82	BNF 2025 - medicinal forms
Bortezomib (V)	1	Powder for solution for injection vials	2.5	97.54	eMIT 2024 - DLK037
Bortezomib (V)	1	Powder for solution for injection vials	3.5	55.87	eMIT 2024 - DHA323
Bortezomib (V)	1	1.4 ml solution for injection vials	3.5	48.00	eMIT 2024 - DLK034
Lenalidomide (R) 2.5	21	Tablets	2.5	26.23	eMIT 2024 - DHK054
Lenalidomide (R) 5	21	Tablets	5	31.48	eMIT 2024 - DHA384
Lenalidomide (R) 7.5	21	Tablets	7.5	45.16	eMIT 2024 - DHD054
Lenalidomide (R) 10	21	Tablets	10	27.55	eMIT 2024 - DHA385
Lenalidomide (R) 15	21	Tablets	15	30.76	eMIT 2024 - DHA386

Treatment	Pack size	Form	Quantity per unit (mg)	Cost per pack (£)	Source (pack cost)
Lenalidomide (R) 20	21	Tablets	20	43.27	eMIT 2024 - DHK053
Lenalidomide (R) 25	21	Tablets	25	28.27	eMIT 2024 - DHB148
Dexamethasone (d) IV	10	Ampoule	3.3mg/1ml	3.08	eMIT 2024 - DJA304
Dexamethasone (d) IV	10	Ampoule	3.8mg/1ml	17.32	eMIT 2024 - DFN051
Dexamethasone (d) IV	10	2.0 ml (ampoule)	6.6mg/2ml	3.21	eMIT 2024 - DFN046
Dexamethasone (d) Oral	100	Tablets	2	5.23	eMIT 2024 - DFN010
Dexamethasone (d) Oral	50	Tablets	2	2.38	eMIT 2024 - DFN018
Dexamethasone (d) Oral	30	Tablets	0.5	2.04	eMIT 2024 - DFC048
Dexamethasone (d) Oral	50	Soluble tablets	4	35.97	eMIT 2024 - DFC044
Dexamethasone (d) Oral	50	Soluble tablets	8	71.95	eMIT 2024 - DKD045
Dexamethasone (d) Oral	50	Soluble tablets	2	18.02	eMIT 2024 - DFN044
Dexamethasone (d) Oral	1	150 ml oral solution sugar free (10mg/5ml)	300	36.42	eMIT 2024 - DFC055
Dexamethasone (d) Oral	1	50 ml oral solution sugar free (10mg/5ml)	100	30.80	eMIT 2024 - DFN033
Dexamethasone (d) Oral	1	50 ml oral solution sugar free (20mg/5ml)	200	52.08	eMIT 2024 - DFN034
Dexamethasone (d) Oral	1	150 ml oral solution sugar free (2mg/5ml)	60	4.42	eMIT 2024 - DFC031
Dexamethasone (d) Oral	1	75 ml oral solution sugar free (2mg/5ml)	30	8.35	eMIT 2024 - DFN022
Melphalan (M)	25	Tablets	2	19.89	eMIT 2024 - DHA070
Melphalan (M)	1	Powder for solution for injection vials	50	24.04	eMIT 2024 - DHA179
Prednisolone (P)	28	Tablets	1	0.29	eMIT 2024 - DFC008

Treatment	Pack size	Form	Quantity per unit (mg)	Cost per pack (£)	Source (pack cost)
Prednisolone (P)	28	Oral gastro-resistant tablets	2.5	0.78	eMIT 2024 - DFC024
Prednisolone (P)	28	Tablets	20	19.46	BNF 2025 - medicinal forms
Prednisolone (P)	28	Tablets	2.5	3.94	BNF 2025 - medicinal forms
Prednisolone (P)	28	Tablets	10	9.70	BNF 2025 - medicinal forms
Prednisolone (P)	28	Tablets	30	29.12	BNF 2025 - medicinal forms
Prednisolone (P)	56	Tablets	25	12.78	eMIT 2024 - DFN031
Prednisolone (P)	1	1 ml oral solution sugar-free (10mg/ml)	10	55.73	eMIT 2024 - DFN050
Prednisolone (P)	1	30 mL oral solution bottle (10mg/ml)	300	55.50	BNF 2025 - medicinal forms
Prednisolone (P)	28	Oral gastro-resistant tablets	5	0.91	eMIT 2024 - DFC025
Prednisolone (P)	100	Oral gastro-resistant tablets	1	32.49	BNF 2025 - medicinal forms
Prednisolone (P)	30	Soluble tablets	5	40.70	eMIT 2024 - DFC036
Prednisolone (P)	28	Tablets	5	0.41	eMIT 2024 - DFN040
Prednisolone (P)	10	5.0 ml (vial)	5	8.58	eMIT 2024 - DKD102
Cyclophosphamide (C)	1	Powder	1000	13.11	eMIT 2024 - DHA014
Cyclophosphamide (C)	1	Powder	2000	27.50	eMIT 2024 - DOU014
Cyclophosphamide (C)	1	Powder	500	11.18	eMIT 2024 - DHA016
Cyclophosphamide (C)	100	Tablets	50	46.74	eMIT 2024 - DHA017
Daratumumab (D) SC	1	15.0 mL solution for injection in vial	1800	4320.00	BNF 2025 - medicinal forms

Abbreviations: BNF, British National Formulary; C, cyclophosphamide; d, dexamethasone; D, daratumumab; eMIT, electronic market information tool; Isa, isatuximab; IV, intravenous; M, melphalan; MIMS, Monthly Index of Medical Specialities; NPC, National Product Code; P, prednisone; R, lenalidomide; SC, subcutaneous; V, bortezomib.

Table 28. List prices of subsequent treatments (Table 109 in CS, Appendix I)

Treatment	Pack size	Form	Quantity per unit (mg)	Cost per pack (£)	Source (pack cost)
Bortezomib (V)	1	Powder for solution for injection vials	1	217.82	BNF 2025 - medicinal forms
Bortezomib (V)	1	Powder for solution for injection vials	2.5	97.54	eMIT 2024 - DLK037
Bortezomib (V)	1	Powder for solution for injection vials	3.5	55.87	eMIT 2024 - DHA323
Bortezomib (V)	1	1.4 ml solution for injection vials	3.5	48.00	eMIT 2024 - DLK034
Lenalidomide (R) 25	21	Tablets	25	28.27	eMIT 2024 - DHB148
Dexamethasone (d) Oral	100	Tablets	2	5.23	eMIT 2024 - DFN010
Dexamethasone (d) Oral	50	Tablets	2	2.38	eMIT 2024 - DFN018
Dexamethasone (d) Oral	30	Tablets	0.5	2.04	eMIT 2024 - DFC048
Dexamethasone (d) Oral	50	Soluble tablets	4	35.97	eMIT 2024 - DFC044
Dexamethasone (d) Oral	50	Soluble tablets	8	71.95	eMIT 2024 - DKD045
Dexamethasone (d) Oral	50	Soluble tablets	2	18.02	eMIT 2024 - DFN044
Dexamethasone (d) Oral	1	150 ml oral solution sugar free (10mg/5ml)	300	36.42	eMIT 2024 - DFC055
Dexamethasone (d) Oral	1	50 ml oral solution sugar free (10mg/5ml)	100	30.80	eMIT 2024 - DFN033
Dexamethasone (d) Oral	1	50 ml oral solution sugar free (20mg/5ml)	200	52.08	eMIT 2024 - DFN034
Dexamethasone (d) Oral	1	150 ml oral solution sugar free (2mg/5ml)	60	4.42	eMIT 2024 - DFC031
Dexamethasone (d) Oral	1	75 ml oral solution sugar free (2mg/5ml)	30	8.35	eMIT 2024 - DFN022
Thalidomide (T)	28	Capsule	50	280.62	BNF 2025 - medicinal forms

Treatment	Pack size	Form	Quantity per unit (mg)	Cost per pack (£)	Source (pack cost)
Cyclophosphamide (C)	1	Powder	1000	13.11	eMIT 2024 - DHA014
Cyclophosphamide (C)	1	Powder	2000	27.50	eMIT 2024 - DOU014
Cyclophosphamide (C)	1	Powder	500	11.18	eMIT 2024 - DHA016
Cyclophosphamide (C)	100	Tablets	50	46.74	eMIT 2024 - DHA017
Daratumumab (D) IV	1	5.0 mL solution for infusion	100	360.00	BNF 2025 - medicinal forms
Daratumumab (D) IV	1	20.0 mL solution for infusion	400	1,440.00	BNF 2025 - medicinal forms
Daratumumab (D) SC	1	15.0 mL solution for injection in vial	1800	4,320.00	BNF 2025 - medicinal forms
Carfilzomib (c)	1	Powder for solution for injection in vial	10	176.00	BNF 2025 - medicinal forms
Carfilzomib (c)	1	Powder for solution for injection in vial	30	528.00	BNF 2025 - medicinal forms
Carfilzomib (c)	1	Powder for solution for injection in vial	60	1,056.00	BNF 2025 - medicinal forms
Pomalidomide (P)	21	Capsule	1	7,551.40	BNF 2025 - medicinal forms
Pomalidomide (P)	21	Capsule	2	7,551.40	BNF 2025 - medicinal forms
Pomalidomide (P)	21	Capsule	3	7,551.40	BNF 2025 - medicinal forms
Pomalidomide (P)	21	Capsule	4	7,551.40	BNF 2025 - medicinal forms
Panobinostat (Pan)	6	Capsule	10	3,492.00	BNF 2025 - medicinal forms
Panobinostat (Pan)	6	Capsule	15	3,492.00	BNF 2025 - medicinal forms
Panobinostat (Pan)	6	Capsule	20	4,656.00	BNF 2025 - medicinal forms
Ixazomib (Ixa)	3	Capsule	2.3	6,336.00	BNF 2025 - medicinal forms
Ixazomib (Ixa)	3	Capsule	3	6,336.00	BNF 2025 - medicinal forms
Ixazomib (Ixa)	3	Capsule	4	6,336.00	BNF 2025 - medicinal forms

Abbreviations: BNF, British National Formulary; c, carfilzomib; C, cyclophosphamide; d, dexamethasone; D, daratumumab; eMIT, Drugs and pharmaceutical electronic market information tool; IV, intravenous; Ixa, ixazomib; MIMS, Monthly Index of Medical Specialties; OBD, on-board device; Pan, Panobinostat; R, lenalidomide; S, Selinexor; SC, subcutaneous; T, thalidomide; V, bortezomib.

Table 29. Concomitant treatment list prices (Table 68 in CS)

Treatment	Pack size	Form	Quantity per unit (mg)	Cost per pack (£)	Source (pack cost)
Paracetamol	24	Tablets	500	1.22	eMIT 2024 - DDG485
Paracetamol	60	Tablets	500	2.68	eMIT 2024 - DDM004
H2 blocker (Cimetidine)	60	Tablets	400	3.82	eMIT 2024 – DAE002
Diphenhydramine	1	150.0 ml oral solution (10mg/5ml)	300	26	MIMS 2024 (Diphenhydramine hydrochlor - Histergan)
Methylprednisolone	1	powder and solvent for solution for injection vials	1000	13.78	eMIT 2024 - DFN009
Aciclovir	25	Tablets	200	0.71	eMIT 2024 - DER023

Section C: Textual clarification and additional points

C1. When carrying out the clinical effectiveness and cost effectiveness systematic literature reviews (SLRs), how many independent reviewers were involved in the quality assessment exercises and how many were involved in the data extraction exercises?

Answer: For the clinical and economic and humanistic SLRs, the following reviewers were involved:

- Quality Assessment: Each included study was subject to a quality appraisal by a single independent reviewer. The quality assessments were then quality checked by a second, senior reviewer.
- Data Extraction: Data extraction was performed by a single reviewer using a standardised Microsoft Excel data extraction sheet. All extracted data were quality checked against the original source article by a second, senior reviewer.

C2. When carrying out the clinical and cost effectiveness SLRs, please specify the search limits applied to the electronic databases.

Answer: The eligibility criteria used in the search strategy for the Clinical SLR are provided in the appendices document of the submission (Table 13; Section D.1.1.2). In-depth search terms for the Clinical SLR are also provided in the appendices document of the submission (Tables 1–12; Section D.1.1.1.4).

The eligibility criteria used in the search strategy for the Economic SLR are provided in the appendices document of the submission (Table 69; Section G.1.3). In-depth search terms for the Economic SLR are also provided in the appendices document of the submission (Tables 65–68; Section G.1.2).

C3. In CS, Table 16, the IMROZ trial OS HR is 0.776 (95% CI: 0.407 to 1.48; p=0.076); however, in CS, Table 18, the unadjusted OS HR is 0.776 (0.548 to 1.099). Which values are correct?

Answer: In CS, Table 16, the IMROZ trial OS HR is 0.776 at the 99.97% confidence interval, as reported in the IMROZ CSR. In CS, Table 18, the unadjusted OS HR is 0.776 (0.548 to 1.099) at the 95% confidence interval and is used to compare the values with the adjusted analyses conducted at the 95% confidence interval. Both values are correct; they are reported at different confidence intervals (CIs). The 99.97% CI provides a wider range (0.407 to 1.48) compared with the 95% CI (0.548 to 1.099), reflecting different levels of statistical confidence.

C4. Please explain the discrepancies in the NMA 95% CrI limits presented in the CS and Appendix D.3.1.7:

a. Fixed-effect PFS NMA results presented in CS, Table 35 (p96) versus CS, Appendix D.3.1.7, Table 25 (p137)

Answer: The results presented in CS, Table 35 were incorrectly derived from the NMA using the global network, which did not exclude comparators not of interest for this appraisal. The correct hazard ratios (HR) and credible intervals (CI) from the network of interest presented in CS, Figure 21 are provided in Table 25 in the appendices. The updated results are provided in Table 30.

Table 30: HRs for IsaVRd versus each treatment – standard PH NMA (PFS)

Treatment	HR (95% CrI)
DRd	[redacted]
Rd	[redacted]
VMP	0.44 (0.25, 0.78)

Abbreviations: CrI, credible interval; DRd, daratumumab, lenalidomide, and dexamethasone; FE, fixed effects; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; NMA, network meta-analysis; PFS, progression-free survival; RE, random effects; Rd, lenalidomide and dexamethasone; VMP, bortezomib, melphalan, and prednisone.
Notes: HR <1 indicates reduced hazard of death for IsaVRd; highlighted indicates statistically significant results.

b. Fixed-effect OS NMA results presented in CS, Table 34 (p96) versus CS, Appendix D.3.1.7, Table 29 (p139)

Answer: The results presented in CS, Table 34 were incorrectly derived from the NMA using the global network, which did not exclude comparators not of interest for this appraisal. The correct hazard ratios (HR) and credible intervals (CI) from the network of interest presented in CS, Figure 21 are provided in Table 29 in the appendices. The updated results are provided in Table 31.

Table 31: HRs for IsaVRd versus each treatment – standard PH NMA (OS)

Treatment	HR (95% CrI)
DRd	[redacted]
Rd	[redacted]
VMP	0.58 (0.32, 1.06)

Abbreviations: CrI, credible interval; DRd, daratumumab, lenalidomide, and dexamethasone; FE, fixed effects; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; NMA, network meta-analysis; PFS, progression-free survival; RE, random effects; Rd, lenalidomide and dexamethasone; VMP, bortezomib, melphalan, and prednisone.
Notes: HR <1 indicates reduced hazard of death for IsaVRd; highlighted indicates statistically significant results.

C5. Please clarify whether the third row in CS, Appendix D.3.2.2.4, Table 47 (p156) should include FIRST trial Rd arm data instead of ALCYONE trial VMP arm data and, if necessary, please update the table.

Answer: The comparison versus Rd using the FIRST trial has been incorrectly placed in the document. It should have been included in the sections related to PFS and OS instead of having a separate section for OS and PFS combined. This would ensure consistency and clarity in presenting the Kaplan-Meier summaries for IsaVRd versus comparators. Additionally, Table 47 (p156) in CS Appendix D.3.2.2.4 should include FIRST trial Rd arm data instead of ALCYONE trial VMP arm data. The updated table is presented below:

Table 32: Kaplan–Meier summary of overall survival – IsaVRd (IMROZ) vs Rd (FIRST)

Treatment (study)	N/ ESS (% of original sample size)	Events	Median survival (95% CI; months)	Difference in RMST (95% CI; months)*
IVRd unadjusted (IMROZ)	265.0	69	NA (NA to NA)	9.11 (5.98 to 12.24)
IVRd weighted (IMROZ)	128.9	42	NA (NA to NA)	6.60 (2.48 to 10.71)
Rd (FIRST)	535.0	289	58.90 (56.14 to 66.21)	Reference

Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; NE, not evaluable; PH, proportional hazards; RMST, restricted mean survival time; VMP, bortezomib, melphalan, and prednisone.
Notes: * Up to the maximum OS time in the IsaVRd arm (69.0 months).

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Myeloma UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Myeloma UK is the only organisation in the UK dealing exclusively with myeloma and related conditions. Our broad and innovative range of services cover every aspect of myeloma from providing information and support, to improving standards of treatment and care through research and campaigning. We are not a membership organisation and rely almost entirely on the fundraising efforts of our supporters. We also receive some unrestricted educational grants and restricted project funding from a range of pharmaceutical companies.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	We have received funding from the manufacturer of the technology (Sanofi) in the last 12 months. Details of our funding is published in our annual report which outlines the funding received in a financial year (Jan-Dec). The table below shows the 2023 income from the relevant manufacturers. Funding is received for a range of purposes and activities namely core grants, project specific work, and gifts, honoraria, or sponsorship.

	Core grant	Research / Project	Donation	Consultancy/ Honoraria	Events	Total
AbbVie Ltd	-	10,000	-	870	-	10,870
Alexion Pharma UK Ltd	-	7,500	-	-	-	7,500
Amgen Ltd	-	20,000	-	-	-	20,000
The Binding Site Ltd	20,000	-	-	437	-	20,437
Bristol-Myers Squibb Pharmaceuticals Ltd	15,000	-	-	-	-	15,000
GlaxoSmithKline UK Limited	-	20,026	-	-	-	20,026
ITECHO Health Ltd	-	6,600	-	-	-	6,600
Janssen-Cilag Ltd	-	15,907	-	260	9,093	25,260
Menarini Stemline UK Limited	-	7,000	-	-	-	7,000
Pfizer Limited	-	-	-	73,448	-	73,448
Stemline Therapeutics Switzerland GmbH	-	-	-	1,451	-	1,451
Sanofi	-	-	-	-	27,990	27,990

	Takeda UK	30,000	-	-	-	29,681	59,681
		65,000	**87,033**	**-**	**76,466**	**66,764**	295,263

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information included in this submission came from the myeloma patients and carers we engage with through our research and services programmes, including: - Semi-structured interviews with myeloma patients who did not get high-dose therapy and stem cell transplantation (HDT-SCT) as part of their initial treatment. These interviews were conducted between August and November 2024, they provide valuable experience and insight data of what it is like living with myeloma. - Analysis of the experiences and views of patients, family members and carers gathered via our Myeloma Infoline, Patient and Family Myeloma Infodays, posts to our online Discussion Forum and insights gathered for earlier appraisals including the recent appraisal for an isatuximab combination. - Analysis of Myeloma UK funded research aiming to understand the patient and carer experience of diagnosis, treatment and living with myeloma - Discussion with clinical experts.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Myeloma is a highly individual and complex cancer originating from abnormal plasma cells in the bone marrow. There is no cure, but treatment can halt its progress and improve the quality of life. The complications of myeloma can be significant, debilitating, and painful; they include severe bone pain, bone destruction, kidney damage, fatigue and a depleted immune system that can lead to increased infections. **"Fatigue, I hadn't really experienced it before. I never had this feeling that your body is not going to work. Even going across the room is a challenge. It is overwhelming."** **"I can handle physical pain, but I can't handle the impact on my mental health. For pain, you can take a painkiller and feel a bit better, but it isn't the same for mood. There are good days and bad days; it is so unpredictable. I know it affects my wife too."** **"It is a strange disease in that it isolates you. COVID made it worse, I am still very wary. My youngest son loves concerts, and he keeps asking me to come. But it is getting there. The crowds. You worry that you will make things worse, but then I worry that I am missing out. I worry that people who don't know much about myeloma think "I should just get a life."** **"The myeloma makes my whole skeleton hurt. I'm disabled now. I can't do much. My husband is my carer, he sees to all my care and looks after me generally. We're toddling on now. I'm just trying to get back a bit of strength. It takes it out of you."** Symptoms are often severe at diagnosis. Many patients are diagnosed with severe complications such as spinal fracture, or reduced kidney function. Therefore, many newly diagnosed patients need support and treatment for associated complications as well as myeloma. This can lead to a higher burden for carers especially when a newly diagnosed is admitted to hospital or struggling with their mobility. **"I was diagnosed with a tumour on my spine. I had a chest MRI because of dysrhythmia, and I got a call from the haematologist that I needed to come to the hospital immediately. I was told I had a plasmacytoma on my T9 that was pressing on my spinal cord. I had lots of tests and biopsies. I remember they opened the radiotherapy department on a Sunday just for me. I was also given a plastazote jacket, so didn't use my spine."** In a survey of 1324 patients and carers, 72% of respondents reported that their myeloma had a high or moderate impact on their quality of life.[1]

[1] Myeloma UK (2022) A Life Worth Living The impact of a delayed diagnosis on myeloma patients' quality of life. Available at https://www.myeloma.org.uk/library/a-life-worth-living/ (Accessed September 2023)

	"Myeloma has had a major impact on my quality of life. No day is the same as you can wake up and find you are in chronic pain and unable to do anything for yourself and have to rely on your carers which has a really negative effect on your mental health. Some of the simplest tasks become impossible to undertake such as going to the bathroom or making a cup of tea… things we take for granted." It is an incurable, relapsing and remitting cancer. The constant possibility of relapse has a huge psychological impact on patients. ***"It is the uncertainty of it, I go every eight weeks to get a blood test and medication, and I think, I hope everything is OK because one day you might not."*** ***"It is always at the back of your mind. Every time I get a new pain, I start to wonder, is it getting older, or is it myeloma."*** ***"It makes you aware of your mortality. For a lot of my life, I felt invincible, but I'm not."*** Patients often talk about having to find a new normal after diagnosis. They have to give up some of the things they love and replace them with other activities or interests. Weakened bones make some sports or activities too risky. The risk of infection, especially when on treatment, means avoiding crowds and busy places. ***"I used to have a boat, but I sold It due to myeloma, I loved sailing, but I am on anti-coagulants because I got blood clots from the treatment. It just felt too risky to go sailing"*** ***"Things just take planning. If you get invited somewhere you have to think about things. I still wear a mask in a shop, it just makes me happier. If we go to the theatre we pick the seats at the end. I still avoid crowds. It does impact on your social life."*** ***"It's a silly thing, but I used to enjoy walking football. But I can't do that anymore because myeloma impacts bones, and any contact sport is not recommended. I do miss it. But due to weakened bones, I don't play."*** To be diagnosed with cancer is devastating, and myeloma is a very complex cancer that doesn't go away. For most patients, treatment is continuous. The ongoing appointments and treatments are hard. and something patients often feel they have to plan things around.

	"When I was diagnosed, I came home with information and consent forms. It was very scary, thank goodness I was a nurse, it must be worse for others." ***"A cancer diagnosis is traumatic, but myeloma goes on for so long and no one really knows about it. People say you look well, but I am not really."*** Patients who don't get HDT-SCT tend to be older or frailer. Many have other medical problems, mobility issues or need help from others with household tasks. Older, frailer patients can experience a higher rate of side effects whilst on treatment and may also experience more symptoms and complications. It is also important to acknowledge that the older patient group are more likely to have a partner or family member with a long-term health condition that they look after. This can add additional stress or burden to the patient or their partner. ***"My husband is very supportive, but I think he is over it. He is hard of hearing. He used to come to all of my appointments, but he couldn't hear anything, so I don't ask him to come now. I go on my own."*** ***"Living with someone with myeloma is difficult at times. It is hard because it often depends on how well you are, and how you are feeling. If you aren't feeling well, it is harder. Harder to be the one with the energy to do things."*** ***"We're moving shortly to assisted living, because if he's not well now, he has a heart condition, because we're 77 and 75, and he wants to feel like we can have help when it's necessary. So, the impact is, well we're getting older and weaker, but it's accelerated that quite a lot."*** Treatment side effects and frequent hospital visits have a social and practical impact on patient's lives, including significant financial implications. Reduction in mobility over time and a perceived increase in reliance on carers and family members also impacts the patient's sense of control. ***"My mobility has decreased over time. In March 2023, I had a steroid induced rupture of the Achilles tendon. It has weakened my legs considerably. I have to use a stick. I was too old for surgery."***

	Living with myeloma is often extremely physically and emotionally challenging for carers, and family members. They are affected in many ways because of both caring and dealing with the day-to-day implications of myeloma. Many in this situation mention changes in their social life, relationships, income, and wider family dynamics. A Myeloma UK study into the experiences of carers and family members found that looking after someone with myeloma has a significant emotional, social and practical impact: - 94% of carers are emotionally impacted and found the uncertainty of myeloma a major factor - 25% of those in work had been unable to work or had to retire early to care for the person with myeloma - 84% always put the needs of their relative or friend with myeloma before their own - Only 42% of carers were not given enough information at diagnosis about how myeloma may affect them[2] ***"I feel angry that I'm not going to get the future I wanted, but the hardest thing to feel is how my life at the moment is in limbo."*** ***"Sometimes it's tiring. Sometimes I feel sad. Sometimes I think about all the hours I have spent at the hospital and how I might have used that time otherwise. But it's all the price of love."*** ***"It is not easy at times, It is hard to know whether to push him or not, to know what is the right thing to do. But I do push him – I don't think he should be sitting all day."***

[2] Myeloma UK (2012) A Life in Limbo: A Myeloma UK research report on the experience of myeloma carers in the UK. Available at https://www.myeloma.org.uk/documents/a-life-in-limbo/ (Accessed September 2023

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers feel fortunate that although myeloma is incurable, it is treatable in most cases. They feel lucky that there are treatments available. Patients are aware that HDT-SCT is generally considered the most effective treatment for myeloma, and that it is thought to deliver on average the deepest responses, and the longest remissions and life expectancy. However, they are also aware that HDT-SCTs are intensive treatments with severe side effects and long recovery times. ***"I always wonder about SCT, I know it isn't a picnic, but it is always something niggling, that maybe I should've had one."*** The Myeloma UK Information Specialists have had 252 calls and 133 emails about HDT-SCT so far this year. This includes calls from patients worried they aren't getting the best treatment, or they are a write-off if they can't have HDT-SCT, However, there are also a significant number of calls from patients worried about whether they will tolerate HDT-SCT due to their age even if their haematologist has put them forward for it. There is a clear need for treatment that delivers comparable outcomes to HDT-SCT for people who can't have or tolerate it. ***"When I started treatment, it was hard to find a good treatment, very difficult to get me stable. That is why I didn't get a stem cell transplant. I was also so responsive to the lenalidomide they didn't want to take me off it. I thought it was my age, but it wasn't."*** ***"I was 75/76 when I was diagnosed, and I was offered a stem cell transplant, but I decided not to go ahead with it. I knew someone who had one and it was very grim for them. I don't have that many years left of my life, and I didn't want to spend one of them in hospital or in recovery. For me, the disadvantages outweighed the benefits"*** *"At first, I was told I was transplant-ineligible, and they were going to put me on a trial, but I wasn't eligible for the trial because I had [health condition] in the past. I was put on DVTD and told I could have SCT. I decided not to go ahead with it – when I looked at the data for people my age, I didn't think there was an advantage to it"* There are currently three main treatments used to treat newly diagnosed myeloma patients who don't have HDT-SCT as their initial treatment. Each of these treatments is used in a slightly different patient cohort.

	• Daratumumab plus lenalidomide and dexamethasone (DRD) is standard of care and the treatment given to most newly diagnosed patients who are ineligible for HDT-SCT. • Bortezomib plus cyclophosphamide and dexamethasone (VCD) is used to treat patients with renal impairment or high-risk myeloma. • Lenalidomide and dexamethasone (RD) is used to treat very elderly, very frail patients and patients who can't attend regular hospital appointments for treatment. We believe the new isatuximab combination, IsaVRD, would be used instead of VCD or DRD. Patients want treatments which are effective and give them a good quality of life. Therefore, the side effects of current treatments are one of the main disadvantages. In a Myeloma UK patient survey (n=793), 97% of myeloma patients reported experiencing at least one side effect (n=773). Myeloma patients reported an average of 11 side-effects (standard deviation=6). A 'lack of energy, weakness, and fatigue' and 'tingling in hands or feet / nerve damage (peripheral neuropathy)' and gastrointestinal issues were the most frequently reported side-effects.[3] The side effects patients felt had the highest impact on their lives were pain (e.g. back pain, rib pain, or pain in other places), recurrent infections and lack of energy, weakness or fatigue.[3] ***"I do get tired tiredness, but I go to bed quite early, if I am in the house I lie down for a while. If I try to sit and watch TV, I nod off now and again. "*** ***"I am far more lethargic than I was, I think it goes with the drug cycles. On the week I am off treatment I feel much better."*** ***"The treatment I am on is effective, but it isn't without its problems. Every time I take it, I don't feel very well the day after. I have abdominal pain and diarrhoea the day after."*** A key disadvantage of available treatments is the addition of dexamethasone. Dexamethasone causes insomnia, mood swings, mania and irritability. We regularly hear from patients and their families about the huge impact this has on their lives.

	"It was the large doses of dexamethasone that scarred me rigid. 40mg. I had mood swings, I couldn't sleep. As a nurse, I knew about high-dose steroids – I said to the doctor – that I might go psycho, but they said that only really happens to people with existing mental health problems. It was scary at the time to have so much. " ***"Dexamethasone does have an effect. Luckily, I only need to take it once a week now, but I know when I take it, I will have a sleepless night. I also find it affects my mental health – I am really irritable."*** Some patients don't like the continuous nature of current treatments because it means that they have to plan their lives around the treatment and potential side effects. It also makes travelling and holidays harder. ***"I was shocked when I was told the treatment would continue until it stopped working. Psychologically, it is not very good when there is no end to it."***
8. Is there an unmet need for patients with this condition?	Yes. Myeloma is incurable and current treatments don't work for all patients. There is a need for innovative treatments which deliver deeper responses, longer remission times and extended life expectancy. This is particularly true of treatment for newly diagnosed myeloma patients because the first remission is often the deepest, longest remission and the period when a patient's quality of life is highest. Each additional line of treatment is associated with worse outcomes; remission times decrease and side effects increase. Treatments often become less effective and harder to tolerate with every relapse. Over time, myeloma evolves, becoming more resistant to treatment, and patients get older, frailer and have more comorbidities. First remission is therefore widely held as the best opportunity to gain the best response with the longest time until disease progression. It is also the point in their disease where many patients will have the best quality of life post-diagnosis because their burden of treatment and illness is less than patients who are multiply relapsed. It is also important to note that not all patients receive treatments beyond first line.[4]

[3] Myeloma UK (2024) Unmet need research: Diagnosing myeloma and its related conditions earlier and better, data on file

[4] Yong, K., et. al. (2016). Multiple myeloma: patient outcomes in real-world practice. British journal of haematology, 175(2), 252–264.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We know from our engagement that patients value treatments which put their myeloma into remission for as long as possible, prolong their life and allow them to enjoy a normal day-to-day life. .[5] The IMROZ trial showed that IsaVRD delivers these benefits. In the trial, the overall response rate was 91%. 74% of patients achieved a complete response or better. After 5 years, 63% of patients who got IsaVRD were still in remission compared to 45% of patients who got VRD. After 5 years, 72% or patients who got IsaVRD were still alive compared to 66% of patients who got VRD.[6] Overall adding isatuximab to bortezomib, lenalidomide and dexamethasone did not increase overall toxicity. The adverse events were clinically manageable and consistent with the known toxicities of isatuximab, bortezomib, lenalidomide and dexamethasone. If approved, IsaVRD would be the first quadruplet for newly diagnosed, transplant ineligible myeloma patients. It contains four drugs that target and kill myeloma cells in completely different ways. Combination treatments are more effective than monotherapies. Myeloma has genetically distinct clones, and the variation in treatment susceptibility between clones is one of the main causes of relapse and treatment resistance in myeloma. Therefore, it is best practice to use combination treatments containing multiple drugs with different mechanisms of action to treat myeloma with triplet and quadruplet combinations are now standard therapy in myeloma. Quadruplets like IsaVRD result in higher response rates, reducing the risk of quickly switching treatments. Having a treatment option with high response rates improves the quality of life of patients, reducing the anxiety associated with relapse and worry that the next treatment won't work for them. Quadruplets also often provide more flexibility to manage side effects. There are four drugs to work with. If a patient experiences side effects due to one of the drugs, its dose can be easily adjusted. However, with monotherapies and doublets severe side effects, often leads to treatment discontinuation, which is devastating for patients. Reaching complete response, having undetectable levels of paraprotein is desirable for patients and has a huge psychological impact. ***"When you have low levels of paraproteins getting your monthly blood test is more stressful. The levels fluctuate. When they are higher you start worrying about relapse. When your paraproteins are undetectable the results are clear."***

	"The aim of all treatments is to reduce the paraproteins, so you need something that does that. But it also depends on the side effects. It is also about quality of life at the end of the day." We know from speaking to patients who have been treated with isatuximab that the drug is considered effective with manageable side effects. ***"I have been able to continue to live a comparatively good life. I have had no side effects, and my bloods remain stable to date."*** ***"I can do my normal range of activities - go walking, rock climbing, socialising, and do all my housework. I also work part time."*** ***"I am in good health (apart from myeloma) and means I can almost stop worrying about this disease and get on with life and look long term instead of short term."***

[5] Postmus, D., et. al. (2018). Individual Trade-Offs Between Possible Benefits and Risks of Cancer Treatments: Results from a Stated Preference Study with Patients with Multiple Myeloma. The oncologist, 23(1), 44–51.

[6] Facon, T., et. al (2024) Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. New England Journal of Medicine.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	There are three factors that patients typically consider when thinking about treatments – efficacy, side effect profile and ease of administration. The order of priority varies based on personal preference.[7] As with all anti-myeloma treatments, side effects are a disadvantage. Patients value treatments with few mild side effects that stop when treatment ends. However, in practice, patients accept varying levels of toxicity in a treatment, depending on the stage of their myeloma and whether it delivers a good survival benefit. When discussing the treatment there was some concern about the intensity of the regimen and level of complexity and toxicity that a quadruplet combination might bring. Patients are also aware that the type and level of side effects people experience varies and there is no way to know what a treatment is really like until you have it. For this reason, patients would go with the treatment that is considered the most effective/best treatment or the treatment recommended by their haematologist. **"Not everyone has the same side effects, so you have to trust the doctor. Some people get really ill with the treatment. You just don't know."** The mode of administration, with regular trips to the hospital for an infusion, was considered a disadvantage by some patients. This does mean taking time out of the day to attend hospital. For some patients there are cost/capability issues associated with this, and it can place an additional burden on carers who may have to accompany the patient to hospital. However, our patient engagement has shown that there are also patients who welcome their treatment being delivered in the safety of a hospital environment and the opportunity to interact with clinical staff and other patients. **"It is nice to speak to someone in the same boat, I often talk to people while waiting."**

[7] Fifer, S, et. al. (2020) Myeloma Patient Value Mapping: A Discrete Choice Experiment on Myeloma Treatment Preferences in the UK, Patient Preference and Adherence, 14, 1283-1293

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	For newly diagnosed myeloma patients it is clinical practice to assess their fitness level and tolerability for HDT-SCT. There are a small number of patients who will exist at the border of being eligible/ineligible for a stem cell transplant. They may feel anxious about undergoing an intensive procedure such a stem cell transplant or the period of isolation. There are also patients for whom HDT-SCT is not a viable option due to a limited support network, existing care responsibilities or financial worries. If this treatment were to be approved, it would give this group greater choice and re-assurance that they can receive an effective treatment. ***"I can still go back and do a stem cell transplant, but I am not too sure if I want to. I am not too keen on the isolation. No proper evaluation has been done to compare a stem cell transplant against the newer treatments which are available. They could be just as effective as a stem cell transplant."***

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Newly diagnosed patients with myeloma who are *eligible* for HDT-SCT have access to a quadruplet contain an anti-CD38 monoclonal antibody, a proteosome inhibitor, an immunomodulatory drug and dexamethasone (TA763). We would like to see equity of access to this innovative quadruplet for all newly diagnosed patients with myeloma.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The patient population covered in this appraisal make up almost two thirds of all myeloma patients. They are generally older or frailer/less fit and cannot tolerate intensive treatments such as a stem cell transplant. • There is a clear need for treatment that delivers comparable outcomes to HDT-SCT for people who can't have or tolerate it. Data from the IMROZ trial has shown that patients in the non-intensive pathway can have a near equivalent response to those patients undergoing HDT-SCT. Approving this treatment will provide much needed reassurance that this patient group are receiving the best possible treatment regardless of their age or fitness. • Patients should get the most effective treatment option at first line. First remission is widely held as the best opportunity to gain the best response with the longest time until disease progression. It is also the point in their disease where many patients will have the best quality of life post-diagnosis because their burden of treatment and illness is less than patients who are multiply relapsed. • If approved, IsaVRD would be the first quadruplet for newly diagnosed, transplant ineligible myeloma patients. It contains four drugs that target and kill myeloma cells in completely different ways. Combination treatments are more effective than monotherapies. • Adding isatuximab to bortezomib, lenalidomide and dexamethasone did not increase overall toxicity.

Thank you for your time.

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Single Technology Appraisal

Isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **31st March 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating untreated multiple myeloma when a stem cell transplant is unsuitable and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Jaimal Kothari
2. Name of organisation	Oxford University Hopsitals NHS Foundation Trust
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with untreated multiple myeloma when a stem cell transplant is unsuitable? ☐ A specialist in the clinical evidence base for untreated multiple myeloma when a stem cell transplant is unsuitable or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	nil

8. What is the main aim of treatment for untreated multiple myeloma when a stem cell transplant is unsuitable? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Initially it is to stop and ideally reverse any organ damage associated with the cancer (such as renal dysfunction, anaemia and bone disease), return these organs to health, and put the myeloma into remission. Treatment then generally continues to maintain the remission, and the treatment should be applied in a way that treatment related side effects are minimised, and quality of life is as good as it can be.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Something that improves organ function and disability, and improves quality of life. This is usually achieved by at least a partial response (>50% reduction in paraprotein).
10. In your view, is there an unmet need for patients and healthcare professionals in untreated multiple myeloma when a stem cell transplant is unsuitable?	Yes, there are many patients who do not respond as well as they could and patient with higher risk disease do not do well with current approaches
11. How is untreated multiple myeloma when a stem cell transplant is unsuitable currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	There are local, national and international guidelines. The UK standard of care for the majority of patients is daratumumab, lenalidomide and dexamethasone (DRD), which at least 2/3 of patients will receive. A smaller proportion of patients will receive lenalidomide and dexamethasone , and a small proportion may receive bortezomib based therapy upfront (eg VD, or VCD) The technology would mean that the group of patients receiving DRD or bortezomib based would likely be treated with Isa-VRD (at least 70-80% of them)
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	There is a change requiring an IV infusion of an antibody (Isatuximab), current approaches use a subcutaneous injection for the antibody (daratumumab). There is also an additional subcutaneous injection for the new technology (bortezomib). So there is a net excess of an extra IV infusion compared to current technology

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The treatment will be given in chemotherapy day units or on haematology wards. No new technology or training is required. All the drugs in the technology are widely used in haematology in the NHS (just not together)
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, I would expect this new therapy to prolong remission for a longer period of time than currently available therapies, reduce the need for treatments at relapse
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This approach would be less suitable for older, frailer patients with comorbidities, and more effective and deliverable for certain groups of patients, eg those that present with significant renal failure, and those with cytogenetically higher risk disease
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Monitoring is broadly the same , and the all the drugs in the combination are already used in the NHS in a different way (but just not together). A practical consideration will be the requirements for cannulaes for IV administration of Isatuximab.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes, standardised criteria for what counts as symptomatic myeloma that requires initiation of therapy. Stopping criteria – at progression (also standardised), or intolerance – which is more nuanced and based on clinical factors as well as patient and physician preferences

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No, they will likely be included in the QALY calculation
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The technology is a step change, the 4 drug combination is offering unparalleled disease control for this group of patients, longer remissions, less risk of relapse and for a select group of patients, it may well be that they only end up requiring one therapy , with patients not dying from relapsing myeloma The unmet needs that are addressed are common ones in myeloma – the requirement for better therapies that control the disease for longer, as patients inevitably relapse
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As all chemotherapy combinations, there are adverse events/side effects caused by this chemotherapy combination, including infections, neuropathy, fatigue etc. However, these are well understood, and manageable with dose reductions, treatment pauses etc. As per all therpy combinations , significant morbidity and death is a risk, and is reflected in the data (and also the data of comparators)
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	The comparator arm against the isatuximab combination (VRD) in the main trial (IMROZ) is not used in the UK in the NHS, however there is a wealth of data on VRD and also other combinations that have VRD in them (eg Dara-VRD). The results can be extrapolated by using indirect comparisons against other clinical trials. There is no clinical trial comparing DRD (UK SoC) against Isa-VRD

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The most important outcomes were measured in the trials – overall survival, progression free survival, time to next treatment, toxicities were appropriately graded and measured. PFS does not always predict overall survival, but MRD negativity is a good surrogate for overall survival, has been shown in multiple myeloma clinical trials No new adverse event above which were in the trials have come to light
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA917, TA587 and TA228?	no
23. How do data on real-world experience compare with the trial data?	There is very limited real world data, as the Isa-VRD combination has only recently been approved.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could	No equity issues identified

• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The new technology offers a potential new standard of care for myeloma patients where stem cell transplant is unsuitable
The side-effects of the Isatuximab combination are well defined, and usually manageable with appropriate monitoring, dose reductions. This technology will not be suitable for all patients, and frailer, older patients may require different approaches.
The Drugs in the combination are all already widely used within the NHS and well understood, so no new additional resources are required to deliver it
As this combination offers a very long remission for many patients there will be less patients relapsing and requiring further interventions /drug combinations earlier in their treatment pathway
The combination offers potential significant advantages for patients with certain profiles of myeloma, such as patients presenting with renal failure, genetically high risk disease

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with untreated multiple myeloma when a stem cell transplant is unsuitable or caring for a patient with this condition. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **18th April.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Part 1: Living with this condition or caring for a patient with untreated multiple myeloma when a stem cell transplant is unsuitable

Table 1 About you, untreated multiple myeloma when a stem cell transplant is unsuitable, current treatments and equality

1. Your name	**Frances McGauran**
2. Are you (please tick all that apply)	☒ A patient living with multiple myeloma who has not received the treatment being evaluated. ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with untreated multiple myeloma when a stem cell transplant is unsuitable? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Myeloma UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with untreated multiple myeloma when a stem cell transplant is unsuitable? **If you are a carer (for someone with untreated multiple myeloma when a stem cell transplant is unsuitable) please share your experience of caring for them**	Knowing myeloma is treatable but incurable living with smouldering myeloma for 8 years felt like living with a gently ticking time bomb which ticked much louder when a blood test, clinic visit or telemed call was due. Then I felt the fear and apprehension days before the date. If a certain nurse took my bloods then it would be fine. You cling onto any superstition to give a feeling of control. I live alone and am a worrier. I told medical staff that I wanted no information about future steps. For 8 years I coped by never reading any of the hospital summaries sent to me. What is seen cannot be unseen. What is heard cannot be unheard. There was no outward sign of its existence and no pain but I knew it was there, lurking. For me, although I wasn't in denial, ignorance is bliss and I prefer to deal with situations as and when they arise. The other way I tried to cope with the uncertainty was to pretend that whatever happened it would be an adventure albeit it not one I would have chosen. I also started regular acupuncture as I wanted a holistic approach to counteract the pharmaceuticals I was taking and someone who had paid time in which to listen. For 8 years I was living an uneasy will it or won't it existence. When I was told that my myeloma had become active it was almost a relief because the worst had finally

	happened. I was even able to start reading those hospital letters because they weren't telling me anything new. I had no symptoms of myeloma but the side effects of my first treatment (Daratumumab) which I began in March 2024 were unpleasant and made living with it much harder. I felt unwell every morning and was unable to make any commitments having to cancel many arrangements, some really important to me. I have always been very active so this came hard and I started to feel I just wasn't me anymore. Some friends slipped away because I wasn't well enough to share their activities. Because I feel tired I'm often in bed by 8.30. It felt like living in a parallel universe. This was not helped by the fact that I needed a hip replacement and was in severe pain. Surgery finally happened on 31/12/24. Since 7 March I have been on Bortezomib. So far any side effects seem minimal so it feels less obviously stressful. Living with it is easier if there are fewer side effects of treatment, you can lead a fuller life though not one free of anxiety which comes from the permanent fear of the disease advancing and knowing that infections are much more likely so I always wear a mask in crowded places which can feel embarrassing at times.
7a. What do you think of the current treatments and care available for untreated multiple myeloma when a stem cell transplant is unsuitable on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	As a patient I am lucky to live close to a Centre of Excellence for cancer so I am confident that I am getting the best treatment. I am lucky that my chemo is administered via subcutaneous injection which takes scarcely a minute. I also have a lot of pills to take at home but am given a chart so I know what to take and when. However, it is sometimes difficult to remember whether certain tablets are provided by the chemo unit or my GP surgery. I have no carers as I live alone. I keep my two adult children up to date and they are relieved and impressed by what I tell them.

8. If there are disadvantages for patients of current NHS treatments for untreated multiple myeloma when a stem cell transplant is unsuitable (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The disadvantages for some people could be the frequency of administration if they live a long way away. The biggest disadvantage would be if the side effects of treatment outweigh the benefits. If you feel really unwell - fatigue, nausea, weakness, lack of motivation and brain fog - this is very isolating and prevents you from doing most of the things you would normal enjoy and greatly reduces the ability to socialise. It would also be difficult for severely needle phobic patients.
9a. If there are advantages of isatuximab with bortezomib, lenalidomide and dexamethasone over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does isatuximab with bortezomib, lenalidomide and dexamethasone help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	I am not on isatuximab but as I stated under question 8 side effects of treatment are very important so if isatuximab in combination means less side effects then this should be considered an advantage. I would also like to again mention the administration of treatment if subcutaneous would be an advantage.
10. If there are disadvantages of isatuximab with bortezomib, lenalidomide and dexamethasone over current treatments on the NHS please describe these. For example, are there any risks with isatuximab with bortezomib, lenalidomide and dexamethasone? If you are concerned about any potential side effects you have heard about, please describe them and explain why	No comment as unknown.

11. Are there any groups of patients who might benefit more from isatuximab with bortezomib, lenalidomide and dexamethasone or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Regardless of the treatment, patients who are very confused or would find it hard to understand the need for diagnostics and treatment may just find it all too overwhelming but would the effect of not treating them be worse?. Patients with severe mental illness may refuse treatment and cannot be forced. Presumably, this treatment would not be considered appropriate for endstage patients. Adherers of certain religions may find aspects of some treatments unacceptable. e.g. some Muslim women would not bare their stomach in public for the subcutaneous injection. Jehovah's Witnesses refuse all blood products. Needle phobic patients would find this challenging
12. Are there any potential equality issues that should be taken into account when considering untreated multiple myeloma when a stem cell transplant is unsuitable and isatuximab with bortezomib, lenalidomide and dexamethasone? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	Hopefully treatment would be based purely on medical criteria and suitability for treatment and not be limited by age or race etc. the patient or his/her advocate should be fully involved in any decision making

More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	No

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Medical staff need to take care to share with the patient only what the patient wants to know.some patients are keen to know everything about the disease and its progression and others like me prefer to face things as and when.

- This is not a criticism but treatment focuses very much on pharmacological solutions to the detriment of a holistic approach. There is the internet to research possibilities but not everyone has access. In Oxford we have Maggies Centre which goes some way to providing this but again it is not easily accessible to all. It is left very much up to the individual to find their own way.

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EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Isatuximab in combination with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 170787

Completed 20th February 2025

CONTAINS [redacted] DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title:	Isatuximab in combination with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]
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Date completed:	20th February 2025

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 170787.

Acknowledgements: The authors would like to thank Dr Faye Sharpley, Consultant Haematologist, The Christie NHS Foundation Trust, who provided feedback on a draft version of the report.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Declared competing interests of the authors: In the last 3 years, Dr Moss received speaker fees from Abbvie. Dr Sharpley received consultancy fees from Pfizer, fees for attendance at a symposium from Menarini Stemline, fees for organising education from Hartley Taylor and speaker fess from AstraZeneca, Menarini Stemline and Johnson and Johnson.

This report should be referenced as follows: Greenhalgh J, Mahon J, Harvey R, Beale S, Boland A, Dundar Y, Marsden A, Moss K**.** Isatuximab in combination with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]: A Single Technology Appraisal. LRiG, University of Liverpool, 2025

Contributions of authors:

Janette Greenhalgh	Project lead, critical appraisal of the clinical evidence and supervised the final report
James Mahon	Critical appraisal of the economic evidence
Rebecca Harvey	Critical appraisal of the statistical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Yenal Dundar	Critical appraisal of the company search strategy
Ashley Marsden	Critical appraisal of the company submission
Kat Moss	Clinical advice and critical appraisal of the clinical evidence

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LIST OF ABBREVIATIONS

AE	Adverse event
ASCT	Autologous stem-cell transplant
CD38	Cluster of differentiation 38
CI	Confidence interval
CS	Company submission
CSR	Clinical study report
d	Dexamethasone
DRd	Daratumumab with lenalidomide and dexamethasone
DVTd	Daratumumab with bortezomib, thalidomide and dexamethasone
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer core quality of life 30-item questionnaire
EQ-5D-5L	EuroQol-5 Dimensions-5 Level
EAG	External Assessment Group
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
Isa	Isatuximab
ICER	Incremental cost effectiveness ratio
IMROZ	The key trial discussed in the company submission
IPCW	Inverse probability of censoring weighting
IPD	Individual patient data
IPW	Inverse probability weighting
IsaRd	Isatuximab, lenalidomide and dexamethasone
IsaVRd	Isatuximab, bortezomib, lenalidomide, and dexamethasone
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
K-M	Kaplan-Meier
MAIC	Matching-adjusted indirect comparison
MHRA	Medicines and Healthcare products Regulatory Agency
MM	Multiple myeloma
MRD	Minimal residual disease
NCRAS	National Cancer Registration and Analysis Service
NDMM	Newly diagnosed multiple myeloma
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reached
OS	Overall survival

PFS	Progression-free survival
PPS	Post-progression survival
QALY(s)	Quality adjusted life year(s)
QLQC30	EORTC Core Quality of Life questionnaire
QLQ-MY20	Myeloma module quality of life questionnaire
QoL	Quality of life
R	Lenalidomide
RCT	Randomised controlled trial
Rd	Lenalidomide and dexamethasone
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of product characteristics
SVd	Selinexor, bortezomib, dexamethasone
TA	Technology appraisal
TE	Transplant eligible
TI	Transplant ineligible
TI-NDMM	Transplant ineligible-newly diagnosed multiple myeloma
TEAE	Treatment-emergent adverse event
TTD	Time to treatment discontinuation
VAS	Visual analogue scale
VCd	Bortezomib with cyclophosphamide and dexamethasone
VMP	Bortezomib, melphalan and prednisone
VRd	Bortezomib, lenalidomide and dexamethasone

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making.

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 provides an overview of key modelling assumptions that have the greatest effect on the incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained. Sections 1.3 to 1.5 explain the key issues identified by the EAG in more detail. Key cost effectiveness results are presented in Section 1.6.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table A Summary of the EAG's key issues

Issue	Summary of issue	Report sections
Issue 1	IMROZ trial comparator	2.4.1
Issue 2	IMROZ trial data are immature	2.4.1
Issue 3	Company ITCs	3.8
Issue 4	Overall survival generated by the company model	6.3
Issue 5	Distributions used by the company: OS and PFS	6.3
Issue 6	Subsequent treatment costs	6.4
Issue 7	Utility values	6.5

EAG=External Assessment Group; ITC=indirect treatment comparison; OS=overall survival; PFS=progression-free survival

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a QALY. An ICER per QALY gained is the ratio of the extra cost for every QALY gained.

In response to clarification questions B1 to B4, the company provided cost effectiveness results for Scenario A (60 months of IMROZ trial data). The EAG considers that whilst Scenario A results were not generated in quite the way anticipated by the EAG, these results are still more informative than company base case results (presented in the CS). Therefore, EAG corrections have all be applied to Scenario A results; these results were generated using list prices for all drugs.

The company OS and PFS estimates for patients treated with IsaVRd and comparators were generated using methods that were overly complex. In addition, the EAG has the following concerns:

- OS and PFS gains for patients treated with IsaVRd may be over-estimates
- compared to treatment with DRd, the EAG considers that there is insufficient clinical effectiveness evidence to support an OS gain for patients treated with IsaVRd
- the utility gain in the PFS health state may be an over-estimate
- subsequent treatment costs for patients treated with IsaVRd may be too low

The company base case cost effectiveness results (presented in the CS) showed that the QALY gain for patients treated with IsaVRd versus DRd was not substantial; company clarification base case (Scenario A) QALY gains and EAG preferred base case QALY gains were even lower. Relative cost effectiveness is therefore very sensitive to IsaVRd and DRd (commercially confidential) drug costs

1.3 The decision problem: summary of the EAG's key issues

Issue 1 IMROZ trial comparator

Report section	2.4.1
Description of issue and why the EAG has identified it as important	The IMROZ trial comparator (VRd) has not been appraised by NICE, is not listed as a comparator in the final scope issued by NICE and is not used in the NHS. It was, therefore, necessary for the company to carry out ITCs to generate clinical effectiveness evidence for the comparison of IsaVRd versus DRd, VMP, Rd and VCd.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	None
What additional evidence or analyses might help to resolve this key issue?	None

DRd=daratumumab plus lenalidomide plus dexamethasone; ITC=indirect treatment comparison; IsaVRd=isatuximab plus bortezomib plus lenalidomide plus dexamethasone; NICE=National Institute for Health and Care Excellence; Rd=lenalidomide plus dexamethasone; VCd=bortezomib with cyclophosphamide and dexamethasone; VMP=bortezomib, melphalan and prednisone; VRd=bortezomib, lenalidomide and dexamethasone

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 IMROZ trial data are immature

Report section	2.4.1
Description of issue and why the EAG has identified it as important	The trial results reported in the CS were generated using data from the September 2023 data cut. At this timepoint, median follow-up was 59.73 months; median PFS had not been reached in the IsaVRd arm and median OS had not been reached in either the IsaVRd or the VRd arms. The company expects new data to become available in 2025 (Q1 or Q2).
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	None
What additional evidence or analyses might help to resolve this key issue?	None

CS=company submission; IsaVRd=isatuximab plus bortezomib plus lenalidomide plus dexamethasone; OS=overall survival; PFS=progression-free survival; VRd=bortezomib, lenalidomide and dexamethasone

Issue 3 Company ITCs

Report section	3.8
Description of issue and why the EAG has identified it as important	The company has carried out NMAs and unanchored ITCs (MAIC [constant HR and time-varying HR] and IPW) to generate clinical effectiveness evidence for the comparison of IsaVRd versus DRd, VMP, Rd and VCd. The EAG highlights that unanchored ITC approaches rely on strong assumptions that are difficult to satisfy, including the assumption that all potential prognostic factors and treatment effect modifiers are accounted for and included in the model. It was not possible to adjusted for all important prognostic factors/treatment effect modifiers. This could have introduced bias due to unmeasured confounding; clinical advice to the EAG is that the extent of any bias is unknown. Despite this limitation, the EAG agrees with the company that MAIC and IPW results are more robust than company NMA results.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	None
What additional evidence or analyses might help to resolve this key issue?	None

DRd=daratumumab plus lenalidomide plus dexamethasone; EAG=External Assessment Group; IPW=inverse probability weighting; IsaVRd=isatuximab plus bortezomib plus lenalidomide plus dexamethasone; ITC=indirect treatment comparison; MAIC=matching-adjusted indirect comparison; NMA=network meta-analysis; Rd=lenalidomide plus dexamethasone; VCd=bortezomib with cyclophosphamide and dexamethasone; VMP=bortezomib, melphalan and prednisone

1.5 The cost effectiveness evidence: summary of the EAG's key issues

Issue 4 Overall survival generated by the company model

Report section	6.3
Description of issue and why the EAG has identified it as important	• OS modelling for comparator treatments was overly complicated and use of time varying hazard ratios was unnecessary • OS for patients treated with IsaVRd is likely to be optimistic • There is insufficient clinical effectiveness evidence to support the modelling of an OS gain for patients treated with IsaVRd versus DRd
What alternative approach has the EAG suggested?	Scenario A + setting OS for DRd to be equal to OS for IsaVRd
What is the expected effect on the cost effectiveness estimates?	Using list prices, for the comparison of IsaVRd versus DRd treatment with IsaVRd remains dominant Using list prices, for the comparison of IsaVRd versus VMP, Rd and VCd all ICERs per QALY gained remain greater than £100,000
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice on OS for patients treated with IsaVRd and patients treated with DRd

DRd=daratumumab plus lenalidomide plus dexamethasone; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IsaVRd=isatuximab plus bortezomib plus lenalidomide plus dexamethasone; OS=overall survival; QALY=quality adjusted life year; Rd=lenalidomide plus dexamethasone; VCd=bortezomib with cyclophosphamide and dexamethasone; VMP=bortezomib, melphalan and prednisone

Issue 5 Distributions used by the company: OS and PFS

Report section	6.3
Description of issue and why the EAG has identified it as important	The EAG considers that, based on 60 months of IMROZ trial data, it is possible to choose distributions that generate OS estimates and PFS estimates that are more in line with clinician landmark estimates than the estimates generated by distributions chosen by the company
What alternative approach has the EAG suggested?	Scenario A + use Gompertz distribution to model IsaVRd OS Scenario A + use Gompertz distribution to model PFS for patients treated with IsaVRd
What is the expected effect on the cost effectiveness estimates?	Using list prices, for the comparison of IsaVRd versus DRd treatment with IsaVRd remains dominant Using list prices, for the comparison of IsaVRd versus VMP, Rd and VCd all ICERs per QALY gained remain greater than £100,000
What additional evidence or analyses might help to resolve this key issue?	None

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Issue 6 Subsequent treatment costs

Report section	6.4
Description of issue and why the EAG has identified it as important	The company may have underestimated subsequent treatment costs for patients treated with IsaVRd.
What alternative approach has the EAG suggested?	The EAG generated cost effectiveness results for the following scenario: Scenario A + set subsequent treatments cost for patient treated to IsaVRd set the same as subsequent treatment costs for patients treated with DRd
What is the expected effect on the cost effectiveness estimates?	Using list prices, for the comparison of IsaVRd versus DRd treatment with IsaVRd remains dominant Using list prices, for the comparison of IsaVRd versus VMP, Rd and VCd all ICERs per QALY gained remain greater than £100,000
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice on the likely subsequent treatments (and associated costs) for patients treated with IsaVRd

DRd=daratumumab plus lenalidomide plus dexamethasone;
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IsaVRd=isatuximab plus bortezomib plus lenalidomide plus dexamethasone; QALY=quality adjusted life year; Rd=lenalidomide plus dexamethasone; VCd=bortezomib with cyclophosphamide and dexamethasone; VMP=bortezomib, melphalan and prednisone

Issue 7 Utility values

Report section	6.5
Description of issue and why the EAG has identified it as important	Utility values in the post-progression health state are too pessimistic and there is insufficient justification for not using IMROZ trial progressed disease utility values
What alternative approach has the EAG suggested?	Scenario A + use IMROZ trial progressed disease utility value
What is the expected effect on the cost effectiveness estimates?	Using list prices, for the comparison of IsaVRd versus DRd treatment with IsaVRd remains dominant Using list prices, for the comparison of IsaVRd versus VMP, Rd and VCd all ICERs per QALY gained remain greater than £100,000
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice on the health related quality of life of patients in the PFS and post-progression health states

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1.6 Summary of EAG's preferred assumptions and resulting ICER

Table B Probabilistic pairwise results (IsaVRd versus DRd), list prices for all drugs

EAG revisions	Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Costs	QALYs		
A. Company CS base case	[redacted]	[redacted]	**IsaVRd dominates**	[redacted]
B1. EAG preferred base case	[redacted]	[redacted]	**IsaVRd dominates**	[redacted]

CS=company submission; DRd=daratumumab plus lenalidomide plus dexamethasone; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; IsaVRd=isatuximab plus bortezomib plus lenalidomide plus dexamethasone; PAS=Patient Access Scheme; QALYs=quality adjusted life year; WTP=willingness to pay

Table C Probabilistic pairwise results (IsaVRd versus VMP), list prices for all drugs

EAG revisions	Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Costs	QALYs		
A. Company CS base case	[redacted]	[redacted]	**£108,920**	[redacted]
B1. EAG preferred base case	[redacted]	[redacted]	**£127,148**	[redacted]

CS=company submission; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IsaVRd=isatuximab plus bortezomib plus lenalidomide plus dexamethasone; NMB=net monetary benefit; PAS=Patient Access Scheme; QALYs=quality adjusted life year; VMP=bortezomib, melphalan and prednisone; WTP=willingness to pay

Table D Probabilistic pairwise results (IsaVRd versus Rd), list prices for all drugs

EAG revisions	Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Costs	QALYs		
A. Company CS base case	[redacted]	[redacted]	**£188,467**	[redacted]
B1. EAG preferred base case	[redacted]	[redacted]	**£234,285**	[redacted]

CS=company submission; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IsaVRd=isatuximab plus bortezomib plus lenalidomide plus dexamethasone; NMB=net monetary benefit; PAS=Patient Access Scheme; QALYs=quality adjusted life year; Rd=lenalidomide plus dexamethasone; WTP=willingness to pay

Table E Probabilistic pairwise results (IsaVRd versus VCd), list prices for all drugs

EAG revisions	Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Costs	QALYs		
A. Company CS base case	[redacted]	[redacted]	**£125,259**	[redacted]
B1. EAG preferred base case	[redacted]	[redacted]	**£147,788**	[redacted]

CS=company submission; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IsaVRd=isatuximab plus bortezomib plus lenalidomide plus dexamethasone; NMB=net monetary benefit; PAS=Patient Access Scheme; QALYs=quality adjusted life year; VCd=bortezomib with cyclophosphamide and dexamethasone; WTP=willingness to pay

For further details of the exploratory and sensitivity analyses carried out by the EAG, see Section 6 and Appendix 8.1.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The focus of this National Institute for Health and Care Excellence (NICE) appraisal is on isatuximab (Sarclisa™) with bortezomib, lenalidomide and dexamethasone (IsaVRd) as a treatment option for patients with newly diagnosed multiple myeloma (NDMM) who are ineligible for autologous stem cell transplant (ASCT).

In this External Assessment Group (EAG) report, references to the company submission (CS) are to the company's Document B, which is the company's full evidence submission. Additional information has been provided by the company in response to the clarification letter.

In the CS, the company refers to patients who are 'unsuitable for' ASCT and to patients who are 'ineligible' for ASCT. The company considers (company response to clarification question A1) that the terms are interchangeable. The company considers that 'ineligible for transplant' is an accepted term in the clinical community. For consistency, and in line with the wording of the Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation,[1] 'ineligible for ASCT' is used throughout this report.

The population described in the final scope[2] issued by NICE is patients with untreated multiple myeloma (MM) and the term used in the anticipated IsaVRd licence is NDMM. The EAG considers that, for the purposes of this appraisal, the terms NDMM and untreated MM are interchangeable.

2.2 Background

2.2.1 Multiple myeloma

Myeloma is a rare, incurable type of haematological cancer that develops from bone marrow plasma cells. Patients are diagnosed with MM when more than one bone marrow site is affected.[3]

In the UK, myeloma accounts for approximately 2% of cancer cases[4] and 12.4% of haematological malignancies.[5] Between 2017 and 2019, the average number of new cases of myeloma in the UK was 6240. More than 43% of myeloma cases are diagnosed in patients aged ≥75 years and a myeloma diagnosis is rare for patients aged <40.[4] Myeloma is more commonly diagnosed in men than in women. Compared to the White ethnic group, myeloma is more commonly diagnosed in the Black ethnic group, and less commonly diagnosed in the Asian ethnic group.[4] In England, the 5-year and 10-year survival rates for patients with myeloma are 55% and 30%, respectively.[6]

2.2.2 Intervention

The intervention is isatuximab plus bortezomib, lenalidomide and dexamethasone (IsaVRd).

Isatuximab (Isa) (brand name Sarclisa™) is an immunoglobulin G1 (IgG1)-derived monoclonal antibody that binds to a specific extracellular epitope of the cluster of differentiation 38 (CD38) receptor. It is administered as an intravenous (IV) infusion.[7]

Bortezomib (V) is available in brand (Velcade™) and generic forms. Bortezomib is a proteasome inhibitor that is specifically designed to inhibit the chymotrypsin-like activity of the 26S proteasome, ultimately resulting in cancer cell death. Bortezomib is administered as an IV infusion or as a subcutaneous (SC) injection.[8]

Lenalidomide (R) is available in brand (Revlimid ™) and generic forms. It is an immunosuppressant that inhibits proliferation and enhances apoptosis of certain haematopoietic tumour cells (including MM plasma tumour cells, follicular lymphoma tumour cells and those with deletions of chromosome 5), enhances T cell- and natural killer (NK) cell-mediated immunity and increases the number of NK, T and NK T cells. It also has anti-angiogenic and pro-erythropoietic properties. Lenalidomide is an oral treatment.[9]

Dexamethasone (d) is available in generic forms. It is a highly potent and long-acting glucocorticoid. Dexamethasone is administered as an oral tablet or as an IV infusion.[10]

The IMROZ[11] trial is the key source of the company's clinical effectiveness evidence for IsaVRd; the trial comprises an induction phase and a continuous treatment phase. In the intervention arm, during the induction phase, patients receive four cycles of treatment with IsaVRd and, during the treatment phase, patients receive continuous treatment with IsaRd. In the comparator arm, during the induction phase, patients receive four cycles of treatment with VRd and, during the treatment phase, patients receive continuous treatment with Rd. The IMROZ trial IsaVRd treatment regimen is shown in Table 1 and the VRd treatment regimens are shown in Table 2.

Table 1 IsaVRd treatment regimen in the IMROZ trial

Phase	Isatuximab (IV)	Bortezomib (SC)	Lenalidomide (PO)	Dexamethasone (IV or PO)
Induction (n=4) 6-week cycles	10mg/kg	1.3mg/m^2	25mg	20mg
Continuous treatment 4-week cycles	10mg/kg	Not given	25mg	20mg

IV=intravenous; PO=oral; SC=subcutaneous
In the continuous phase, isatuximab frequency is reduced from every 2 weeks to every 4 weeks after 18 cycles of treatment
Source: based on CS, Figure 6

Table 2 VRd treatment regimen in the IMROZ trial

Phase	Bortezomib (SC)	Lenalidomide (PO)	Dexamethasone (IV or PO)
Induction (n=4) 6-week cycles	1.3mg/m^2	25mg	20mg
Continuous treatment 4-week cycles	Not given	25mg	20mg

IV=intravenous; PO=oral; SC=subcutaneous
Source: based on CS, Figure 6

2.3 Company's overview of current service provision

The company has provided details of the current NHS treatment pathway for patients with MM who are ineligible for ASCT, and the proposed positioning of IsaVRd, should it be recommended by NICE (CS, Figure 3). The company has positioned IsaVRd as a first-line treatment (CS, p27). The current first-line treatment options are shown in Figure 1 (adapted from CS, Figure 3). Clinical advice to the EAG is that Figure 1 is generally an accurate representation of first-line treatment options for patients with NDMM who are ineligible for ASCT. Clinical advice to the EAG is that DRd is current standard of care for NHS patients with NDMM who are ineligible for ASCT.

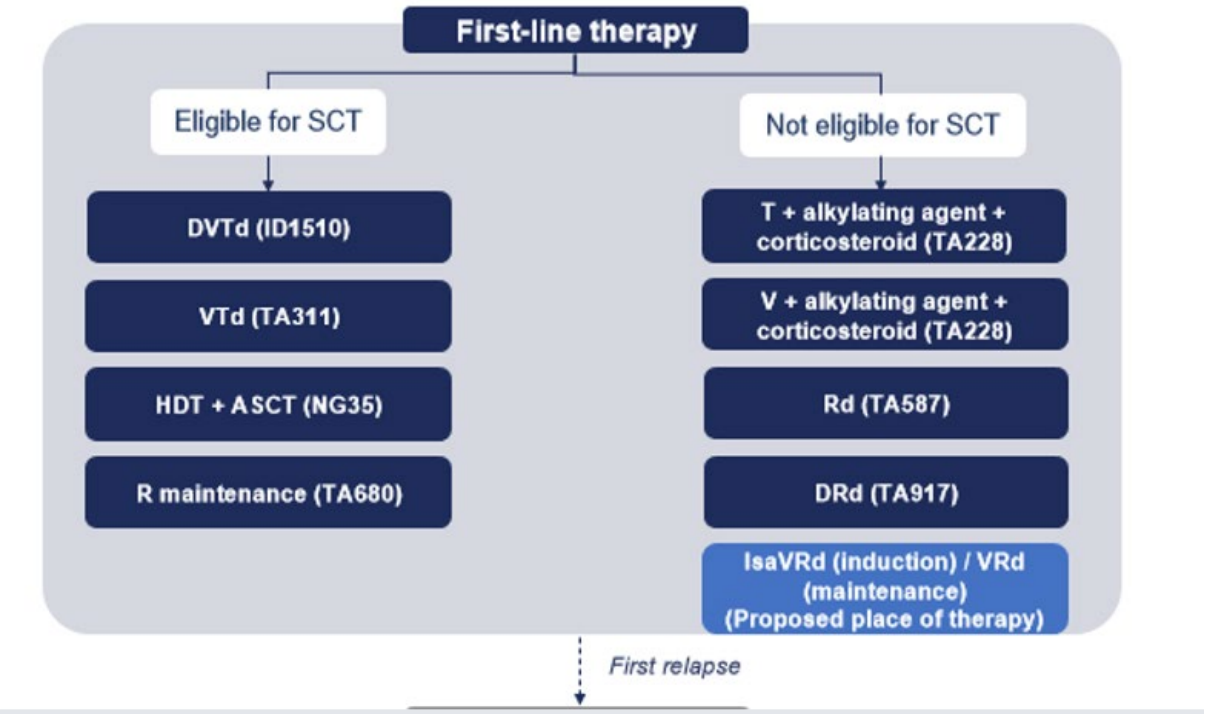


Figure 1 Company's overview of the treatment pathway for multiple myeloma

ASCT=autologous stem cell transplant; d=dexamethasone; D=daratumumab; HDT=high-dose therapy; IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; R=lenalidomide; T=thalidomide; V=bortezomib
Source: Based on CS, Figure 3

2.4 Critique of company's definition of decision problem

A summary of the final scope[2] issued by NICE and the decision problem addressed by the company is presented in Table 3. More information regarding key issues is provided in Section 2.4.1 to Section 2.4.6.

Table 3 Summary of decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Intervention	Isatuximab with bortezomib, lenalidomide and dexamethasone (IsaVRd)	As per scope	As per scope
Population	Adults with untreated MM when stem cell transplant is unsuitable	Adult patients with newly diagnosed active MM who are ineligible for autologous stem cell transplant (ASCT)	As per scope. The EAG considers that untreated MM and newly diagnosed MM refer to the same population. The EAG agrees with the company that unsuitable for transplant and ineligible for transplant (ASCT) are interchangeable terms.
Comparator(s)	• Daratumumab with lenalidomide and dexamethasone (DRd) • Lenalidomide with dexamethasone (Rd) • Bortezomib with alkylating agent and corticosteroid (such as cyclophosphamide and dexamethasone)	• Daratumumab, lenalidomide and dexamethasone (DRd) • Lenalidomide and dexamethasone (Rd) • Bortezomib, cyclophosphamide and dexamethasone (VCd) Bortezomib, melphalan, and prednisone (VMP)	As per scope; VRd (IMROZ trial comparator) is not listed in the final scope[2] issued by NICE as a relevant comparator to IsaVRd.
Outcomes	• OS • PFS • Response rates • TTD • MRD-negative status • AEs of treatment • HRQoL	As per scope	Direct evidence The company has presented IMROZ trial clinical effectiveness evidence for IsaVRd versus VRd for all outcomes listed in the final scope[2] issued by NICE. Indirect evidence The company undertook PFS and OS ITCs to compare the clinical effectiveness of IsaVRd versus DRd, Rd, VCd and VMP. The EAG considers that the company approach to generating evidence to compare the clinical effectiveness of IsaVRd versus DRd, VMP, Rd and VCd was comprehensive.

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Economic analysis	The cost effectiveness of treatments should be expressed in terms of ICERs per QALY gained The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs should be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies should be taken into account. The availability and cost of biosimilar and generic products should be taken into account	A cost-utility analysis was conducted to estimate lifetime costs and health-related outcomes, including incremental cost-effectiveness ratio (ICER) (cost per quality-adjusted life year [QALY]), from the perspective of the NHS and PSS, comparing IsaVRd to DRd, Rd, VCd, and VMP.	As per scope.
Special considerations including issues related to equity or equality	None specified in scope.	Transplant-eligible patients currently benefit from the quadruplet induction therapy of daratumumab plus bortezomib, thalidomide, and dexamethasone (DVTd) (TA763). In contrast, transplant-ineligible patients don't have access to the benefit of a quadruplet therapy. Access to IsaVRd therapy for TI patients would help mitigate this inequality.	The EAG does not consider that the number of treatments in a regimen is an equality issue.

AE=adverse event; ASCT=autologous stem cell transplant; DRd=daratumumab+lenalidomide+dexamethasone; DVTd=daratumumab+bortezomib+thalidomide+dexamethasone; HRQoL=health-related quality of life; ICER=incremental cost-effectiveness ratio; IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; ITC=indirect treatment comparison; MRD=minimal residual disease; NDMM=newly-diagnosed multiple myeloma; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; Rd=lenalidomide with dexamethasone; TTD=time to treatment discontinuation; VCd=bortezomib+cyclophosphamide+dexamethasone; VMP=bortezomib+melphalan+prednisone
Source: CS, Table 1 and EAG comment

2.4.1 Source of direct clinical effectiveness data

The company has presented clinical effectiveness evidence for IsaVRd from the IMROZ trial. The IMROZ trial is an ongoing, international phase III, open-label, randomised controlled trial (RCT) that compares the efficacy and safety of IsaVRd (n=265) with VRd (n=181) in patients with NDMM who are ineligible for ASCT. Patients in the VRd arm whose disease progresses whilst they are in the continuous treatment phase can receive treatment with IsaVRd.

The IMROZ trial comparator (VRd) has not been appraised by NICE and is not used in the NHS.

The IMROZ trial primary endpoint is PFS. The trial results reported in the CS have been generated using data from the 26th September 2023 data cut; at this timepoint, median follow-up was 59.73 months. The company expects (CS, p104) new data to become available in 2025 (Q1 or Q2).

2.4.2 Population

The population recruited to the IMROZ trial matches the population described in the final scope[2] issued by NICE, i.e., adults with NDMM who are ineligible for ASCT. Clinical advice to the EAG is that patients in the IMROZ trial have similar demographic and disease characteristics to NHS patients with NDMM and that the results of the trial are generalisable to NHS patients.

Clinical advice to the EAG is that some NHS patients who are eligible for ASCT choose not to have it (i.e., with no intent for ASCT), and that these patients are generally younger and fitter than patients who are ineligible for ASCT. The company has not presented any specific IMROZ trial evidence for patients with no intent for ASCT.

Clinical advice to the EAG is that, for most NHS patients with NDMM who are ineligible for ASCT, the first-line treatment is DRd. Clinical advice to the EAG is that, for NHS patients with NDMM who are ineligible for ASCT and who have critical renal function (defined as creatinine clearance >30ml/min), the first-line treatment is bortezomib combined with a steroid; the aim of this treatment combination is to improve renal function. Since the IsaVRd regimen includes bortezomib, clinical advice to the EAG is that if IsaVRd were recommended by NICE as a treatment option for NHS patients, it would be an appropriate treatment choice for patients with critical renal function. The EAG highlights that the IMROZ trial excluded patients with critical renal function and, therefore, data are not available to demonstrate the efficacy of treatment with IsaVRd in patients with critical renal function.

2.4.3 Intervention

The intervention is IsaVRd. The dosing regimen for IsaVRd is provided in Table 1.

In January 2025 the MHRA granted regulatory approval for isatuximab in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.[1]

2.4.4 Comparators

The three comparators listed in the final scope[2] issued by NICE are DRd, Rd, and bortezomib with alkylating agent and corticosteroid (such as cyclophosphamide and dexamethasone). The company has provided clinical effectiveness data for all three comparators. For the comparison of IsaVRd versus bortezomib with alkylating agent and corticosteroid, the company has used two treatment regimens, bortezomib+cyclophosphamide+dexamethasone (VCd) and bortezomib+melphalan+prednisone (VMP). Clinical advice to the EAG is that this is appropriate.

The EAG agrees with the company (CS, p20) that, of the three comparators listed in the final scope[2] issued by NICE, the most relevant comparator is DRd. Clinical advice to the EAG and the company is that, in the NHS, DRd is the current standard of care for patients with NDMM. Treatment with Rd is available to patients with NDMM who prefer oral medication and/or who do not want to attend hospital for treatment.

In the absence of direct clinical effectiveness evidence comparing IsaVRd to the any of the comparators specified in the final scope[2] issued by NICE, the company has conducted indirect treatment comparisons (ITC).

2.4.5 Outcomes

The company has provided IMROZ trial (IsaVRd versus VRd) results for all the outcomes listed in the final scope[2] issued by NICE, namely overall survival (OS), progression-free survival (PFS), response rates (including duration of response [DoR] and overall response rate [ORR]), minimal residual disease-negative status (MRD-negative status), adverse events (AEs) and health-related quality of life (HRQoL). Clinical advice to the EAG is that these are the most important outcomes for patients with NDMM.

The IMROZ trial data are immature; median PFS has not been reached in the IsaVRd arm, and median OS has not been reached in either trial arm.

In the absence of head-to-head trials comparing IsaVRd with relevant comparator treatments, the company carried out PFS and OS ITCs to generate comparative clinical effectiveness

data. The EAG considers that the company approach to generating ITC evidence to compare the clinical effectiveness of IsaVRd versus DRd, VMP and Rd was comprehensive. The EAG agrees with the company that matching-adjusted indirect comparison (MAIC) results are likely to be more reliable than NMA results. The EAG has no strong concerns relating to use of IPW to compare the clinical effectiveness of IsaVRd versus VCd.

2.4.6 Economic analysis

As specified in the final scope[2] issued by NICE, the cost effectiveness of treatments was expressed in terms of incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY) gained. Outcomes were assessed over a 29-year time horizon (which the company considered was equivalent to a lifetime horizon) and costs were considered from an NHS perspective.

Several drugs used in the economic analyses are available to the NHS at confidential prices:

- isatuximab: Patient Access Scheme (PAS)
- bortezomib: Medicines Procurement and Supply Chain Price (MPSC)
- daratumumab, carfilzomib, pomalidomide, panobinostat and ixazomib: PAS and Commercial Access Agreement (CAA)

However, all the company and EAG cost effectiveness results presented in this report have been generated using only list prices.

The EAG agrees with the company that a severity weighting was not applicable for this appraisal (see CS, p168).

2.5 Other considerations

The company has highlighted a potential inequality between patients who are eligible for ASCT and patients who are ineligible for ASCT. The company notes that patients who are eligible for ASCT have the option for treatment with the quadruplet induction therapy DVTd, whereas there is currently no quadruplet therapy available to patients who are ineligible for ASCT. The company suggests that if IsaVRd was recommended by NICE as a treatment option for NHS patients, the inequality between patient groups would be addressed. The EAG does not consider that the difference in the number of treatments within a regimen constitutes an equity issue.

3 CLINICAL EFFECTIVENESS

This section provides a structured critique of the clinical effectiveness evidence submitted by the company to support the use of IsaVRd as a treatment option for patients with NDMM who are ineligible for ASCT.

3.1 Critique of the methods of review(s)

The company conducted a systematic literature review (SLR) to identify and select IsaVRd clinical effectiveness evidence. Full details of the company's methods are presented in the CS (CS, Appendix D). The company's literature searches were comprehensive and were completed <6 months before the company's evidence submission to NICE. An assessment of the extent to which the company's SLR was conducted in accordance with the Liverpool Reviews and Implementation Group (LR*i*G) in-house systematic review checklist is presented in Table 4. The EAG considers that the company's systematic review methods were appropriate.

Table 4 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	CS, Appendix D.1.1.2, Table 13
Were appropriate sources searched?	Yes	CS, Appendix D.1 The company's literature searches were comprehensive and were completed <6 months before the company's evidence submission to NICE
Was the timespan of the searches appropriate?	Unclear	The timespan of the searches was not reported in the CS or at clarification (Question C2).
Were appropriate search terms used?	Yes	CS, Appendix D.1.1.1.4
Were the eligibility criteria appropriate to the decision problem?	Yes	CS, Appendix D.1.1.2, Table 16
Was study selection applied by two or more reviewers independently?	Yes	CS Appendix D.1.1.2
Were data extracted by two or more reviewers independently?	Partially	Data extraction was performed by a single reviewer and checked by a second, senior reviewer. (Clarification question C1). The EAG considers this strategy is acceptable.
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	Assessment of all trials was carried out using the minimum criteria recommended by NICE[12]
Was the quality assessment conducted by two or more reviewers independently?	Partially	Data extraction was performed by a single reviewer and checked by a second, senior reviewer. (Clarification question C1). The EAG considers this strategy is acceptable.
Were attempts to synthesise evidence appropriate?	Yes	The company carried out ITCs to generate clinical effectiveness evidence to compare IsaVRd with DRd, Rd, VCP and VMP. The EAG's critique of the company's methods is presented in Section 3.8 of this report

CS=company submission; DRd=daratumumab+lenalidomide+dexamethasone; EAG=External Assessment Group; IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; ITCs=indirect treatment comparisons; Rd=lenalidomide+dexamethoasone; VCP=bortezomib+cyclophosphamide+dexamethasone; VMP=bortezomib+melphalan+prednisone
Source: LR*i*G in-house checklist

3.2 EAG summary and critique of clinical effectiveness evidence

3.2.1 Included trials

The company SLR identified one relevant trial, the IMROZ trial. The IMROZ trial is an ongoing, international, open-label, phase III RCT trial that provides evidence of the efficacy of IsaVRd as a treatment for adult patients with NDMM who are unsuitable for ASCT. The IMROZ trial

comparator treatment is VRd. As noted in Section 2.4.1, VRd is not recommended by NICE for use in the NHS.

The company conducted ITCs to compare the clinical effectiveness of IsaVRD versus DRd, Rd, VCP and VMP. The EAG's summary and critique of the company's ITCs are presented in Section **3.7**. Details of the trials that provided the data that were used in the company ITCs are available in the CS (CS, Appendix D).

3.2.2 Characteristics of the IMROZ trial

A summary of the IMROZ trial design is presented in the CS (Figure 6). The trial consists of an induction phase (4 x 6-weekly cycles) and a continuous phase (4-weekly cycles). Patients in the IsaVRd arm receive induction treatment with IsaVRd followed by IsaRd. Patients in the VRd arm receive induction treatment with VRd followed by Rd. Treatment is continued until disease progression or unacceptable toxicity. Patients in the VRd arm with confirmed disease progression in the continuous phase can cross over to the IsaVRd arm. The treatment regimens administered in the trial are shown in Section 2.2.2 (Table 1 and Table 2) and the CS (Figure 6).

In the IMROZ trial, randomisation was stratified by country (China/not China), age (<70 versus ≥70 years), and Revised International Staging System disease stage (Stage I or Stage II versus Stage III versus not classified). The numbers of patients recruited to the IsaVRd arm and the VRd arms were 265 and 181, respectively. Patients were recruited from 93 sites across 21 countries; most patients were from France (n=78), Czechia (n=52), Turkey (n=47), Australia (n=41) and Greece (n=32). Other countries involved in the IMROZ trial were, Belgium, China, Italy, Japan, Lithuania, Mexico, New Zealand, Poland, Portugal, Russia, Spain, Sweden and USA. No patients were recruited from the UK.

3.2.3 Demographic and disease characteristics of IMROZ trial patients

IMROZ trial baseline patient demographic characteristics and baseline patient disease characteristics are provided in the CS (CS, Table 10 and Table 11). The EAG agrees with the company (CS, p40) that baseline characteristics were balanced between the IMROZ trial arms.

The company confirmed (in response to clarification question A2) that patients with any diagnosis of amyloidosis (i.e. primary amyloidosis or MM with amyloidosis) were ineligible for inclusion in the IMROZ clinical trial. The EAG considers that, therefore, IMROZ trial results should not be generalised to patients with any diagnosis of amyloidosis.

Clinical advice to the EAG is that IMROZ trial patients are generally comparable to NHS patients with NDMM and the IMROZ trial results can be generalised to NHS patients.

3.2.4 Quality assessment of the IMROZ trial

The company conducted a quality assessment of the IMROZ trial using the minimum criteria recommended by NICE.[12] The company's assessment results are presented in the CS (CS, Table 13). The EAG agrees with the company's assessment results and highlights that the use of an independent review committee to assess disease progression outcomes helps to mitigate any potential bias associated with the trial's open-label design. The EAG considers that the IMROZ trial is of good methodological quality with a low risk of bias.

3.2.5 Statistical approach adopted for the analysis of the IMROZ trial data

Information relevant to the statistical approach taken by the company to analyse the IMROZ trial data has been extracted from the Clinical Study Report (CSR),[13] the trial statistical analysis plan (TSAP),[11] the amended clinical trial protocol (28th September 2023),[11] and the CS. A summary of the EAG checks of the pre-planned statistical approach used by the company to analyse data from the included trial is provided in Table 5.

Table 5 EAG assessment of statistical approaches used in the IMROZ trial

Item	EAG assessment	Statistical approach with EAG comments
Were all analysis populations clearly defined and pre-specified?	Yes	The IMROZ trial analysis populations (ITT, safety and crossover) are clearly defined in the CS (Section B.2.4.1 and were pre-specified in the TSAP (TSAP, Section 2.3)
Was an appropriate sample size calculation pre-specified?	Yes	The sample size calculation is presented in the CS (CS, Table 12) and pre-specified in the TSAP (TSAP, Section 1.3)
Were all protocol amendments made prior to analysis?	Yes	The EAG is satisfied that all protocol amendments were made prior to analysis and that the amendments were justified (Protocol, p241 onwards)
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	The IMROZ trial primary outcome is PFS. Key secondary outcomes include OS, response rates, sustained MRD negativity rate (≥12 months), PFS2, TTNT, TTD, safety and HRQoL. Information relating to the primary and secondary outcomes and their analyses are described in the protocol (Protocol, p16 and Section 11.4.4.1, Section 11.4.4.2) and TSAP (TSAP, Section 2.4.4)
Was the analysis approach for PROs appropriate and pre-specified?	Yes	Information relating to the IMROZ trial PROs and linked analyses are described in the TSAP (TSAP, Section 2.4.9)
Was the analysis approach for AEs appropriate and pre-specified?	Yes	Information relating to the AEs and linked analyses are described in the TSAP (TSAP, Section 2.4.4)
Was a suitable approach employed for handling missing data?	Yes	The analyses and summaries of continuous and categorical variables are based on observed data only. Percentages are calculated using the number of patients with non-missing observations in the considered population as the denominator. When relevant, the number of patients with missing data is presented (CS, Table 12 and TSAP, Section 2.5.3)
Were all subgroup and sensitivity analyses pre-specified?	Yes	CS subgroup analyses and sensitivity analyses pre-specified in the TSAP (TSAP, Table 11 and TSAP, Section 2.4.4.2 to Section 2.4.4.3)

AE=adverse event; CS=company submission; EAG=External Assessment Group; HRQoL=health-related quality of life; ITT=intention to treat; MRD=minimal residual disease; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcome; TSAP=trial statistical analysis plan; TTD=time to treatment discontinuation; TTNT=time to next treatment
Source: CS, CSR,[13] trial protocol,[11] TSAP[11]

3.3 IMROZ trial efficacy results

The IMROZ trial primary outcome is PFS. The data cut-off date for the PFS analysis reported in the CS is 26th September 2023 when the median follow-up was 59.73 months. The company expects (CS, p104) new data will become available in 2025 (Q1 or Q2).

The IMROZ trial schedule of planned analyses is event-driven. The IMROZ trial protocol lists three planned interim analyses (when 60%, 75% and 85% of the 222 PFS events have been observed). The data presented in the CS are from the second interim analysis (75%). The cut-off date for the final PFS analysis is planned for approximately 60 months after the first patient was randomised. The cut-off for the final analysis of OS data is when approximately 202 deaths have occurred.

3.4 Key IMROZ trial clinical effectiveness results

PFS and OS results

After 59.73 months of follow-up, median PFS had not been reached in the IsaVRd arm and median OS had not been reached in either of the trial arms (Table 6).

Table 6 IMROZ trial ITT PFS and OS results

Endpoint	IsaVRd (N=265)	VRd (N=181)
Progression-free survival (IRC)		
Median, months	NR (NR to NR)	54.34 (45.207 to NR)
HR (95% CI)	0.596 (0.406 to 0.876) p=0.0005	
Overall survival		
Median, months	NR	NR
Estimated HR (99.9725% CI)	0.776 (0.407 to 1.48) p=0.0760	

CI=confidence interval; IRC=independent review committee; IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; NR=not reached; PFS=progression-free survival; OS=overall survival; VRd=bortezomib+lenalidomide+dexamethasone
Source: CS, Table 14, Table 16

Adjustments for treatment crossover and subsequent treatments

The company conducted post-hoc adjustment analyses to address treatment crossover and the impact of subsequent treatments administered in the IMROZ trial that are not available in the NHS (CS, Section B.2.6.1.3). The EAG agrees with the company (CS, p64) that there is little difference between the adjusted HR and the unadjusted estimated HR results (Table 7).

Table 7 Adjusted OS results

Adjustment	HR (95% CI)
Unadjusted data	0.776 (0.54 to 1.099)
IPCW - crossover	0.729 (0.521 to 1.020)
IPCW - crossover and subsequent treatments not available in NHS clinical practice	0.724 (0.516 to 1.015)

CI=confidence interval; HR=hazard ratio; IPCW=inverse probability of censoring weighting
Source: CS, Table 18

Subgroup analyses (PFS)

Pre-specified subgroups

The results of the IMROZ trial PFS prespecified subgroup analyses are presented in the CS as forest plots, (CS, Figure 17 and Figure 18). The analyses were conducted when at least 10 participants were included in each treatment group within a subgroup (CS, p75). The EAG agrees with the company (CS, p75) that the results for the subgroups are consistent with the overall PFS results; however, many of the subgroup analysis results have been generated using data from small numbers of patients. The EAG highlights that median PFS in the IsaVRd arm has not been reached.

Post-hoc analysis -frail versus non-frail patients

The company conducted a post-hoc analysis of PFS results for frail patients (29%) versus non-frail patients (70%) in the IMROZ trial (CS, p76). Frailty was defined using the International Myeloma Working Group frailty score. For frail patients (CS, Figure 19) the PFS rate in the IsaVRd arm was 55.2% versus 41.3% in the VRd arm (HR=0.584; 95% CI 0.340 to 1.004, p=0.052). For non-frail patients (CS, Figure 20), the PFS rate in the IsaVRd arm was 66% versus 47.3% in the VRd arm (HR=0.593; 95% CI 0.403 to 0.873; p=0.008). The rates of treatment-emergent AEs in the IMROZ trial appear to be similar in frail and non-frail patients (CS, Table 21).

Exploratory analysis- high-risk cytogenetic population

The results of an exploratory analysis of PFS results in patients with high-risk cytogenetic status are presented in the CS (CS, p79). High-risk cytogenetic status was defined as the presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16). The company also assessed PFS outcomes for patients with 1q21+ gain and amplification. The company reports that the outcomes for patients with the high-risk cytogenic disease were consistent with the outcomes for the ITT population. The company was unable to interpret the HR for patients with chromosomal abnormality t(14;16) due to small patient numbers (<10).

Other PFS analyses

Details of the company's PFS sensitivity analysis, multivariate analyses and next generation sequencing MRD status from the IMROZ trial are presented in the CS (CS, Appendix M). The company reports that:

- the results of the PFS sensitivity analyses were all consistent with the primary PFS analysis results.
- the multivariate Cox proportional model demonstrated that the effect on PFS was only related to the addition of isatuximab to VRd.
- A PFS benefit was observed in patients with MRD-negative status compared with those with MRD-positive status in the IsaVRd group, the HR for a PFS event was 0.220 (95% CI: 0.139 to 0.349) for MRD negative vs MRD positive patients in the IsaVRd group.

Summary of secondary endpoints from the IMROZ trial

A summary of secondary endpoints from the IMROZ trial is presented in Table 8. Details are provided in the CS, Section B.2.6.1.4).

Table 8 Summary of secondary endpoints from the IMROZ trial

Endpoint	IsaVRd	VRd
Overall response rate	242 (91.3%)	167 (92.3%)
Time to progression (median)	NR	59.70 months
Duration of response (median)	NR	58.25 months
Time to first response (median)	1.51 months	1.48 months
Time to best response (median)	6.51	5.59
Sustained MRD negativity rate (≥12 months)	46.8%	24.3%
PFS2	31.7%	41.4%
Time to next treatment (median)	NR	63.57 months
Time to treatment discontinuation (median)	[redacted]	[redacted]

IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; NR=not reached; PFS=progression-free survival; VRd=bortezomib+lenalidomide+dexamethasone
Source: CS, Section B.2.6.1.4

3.5 IMROZ trial health-related quality of life

In the IMROZ trial, HRQoL data were collected using the EQ-5D-5L[14] questionnaire, the EORTC QLQ-C30[15] questionnaire and the EORTC QLQ-MY20[16] questionnaire.

EQ-5D-5L

The EAG agrees with the company (CS, p71) that responses to the Health State Utility Index appear to show a trend in favour of the use of isatuximab and, that responses to the Visual Analogue Scale suggest that HRQoL was similar in both treatment arms across the course of the trial. Results of the EQ-5D-5L exercise were mapped to EQ-5D-3L and included in the company cost effectiveness model; they are presented in the CS (CS, Section B.3.4.6).

EORTC QLQ-C30 and EORTC QLQ-MY20

The EAG agrees with the company (CS, p72) that responses to the questionnaires indicate that HRQoL in both treatment arms was similar and remained stable across the trial.

3.5.1 EAG conclusions: HRQoL

The company states (CS, p32) that the addition of isatuximab to VRd improved patient HRQoL as measured by the EQ-5D Health State Utility Index and did not result in any detriment to patient HRQoL as measured by the EORTC QLQ-C30 Global Health Score. The EAG agrees that HRQoL for patients treated with IsaVRd appears to be comparable with the HRQoL reported by patients treated with VRd.

3.6 IMROZ trial adverse events

Information relating to the AEs experienced by patients in the IMROZ trial is presented in the CS (CS, Section B.2.10.1).

The median duration of treatment exposure was 53.16 months (range=0.5 to 68.8) in the IsaVRd arm and 31.28 months (range=0.6 to 67.2) in the VRd arm. Mean and median RDIs for the individual treatment components were similar between the trial arms (CS, Table 40).

Treatment-emergent adverse events

The rates of treatment-emergent adverse events experienced by patients in the IMROZ trial are shown in Table 9 alongside the event rates per patient year.

The company highlights (CS, p99) that:

- The percentage of participants with Grade ≥3 TEAEs was higher in the IsaVRd group (91.6%) compared with the VRd group (84.0%). However, once adjusted for exposure, the rates were similar (1.171 and 0.986 event per patient-year, respectively).
- Grade 5 TEAEs were reported for 29 (11.0%) participants in the IsaVRd group and 10 (5.5%) participants in the VRd group. This difference was largely driven by the difference in treatment exposure (exposure-adjusted rates for Grade 5 TEAEs are 0.031 and 0.019 events per patient year with IsaVRd and VRd, respectively).

Table 9 IMROZ trial treatment-emergent adverse events

	IsaVRd (N=263)		VRd (N=181)	
	n (%)	Event rate per patient year	n (%)	Event rate per patient year
Patients with any TEAE	262 (99.6)	13.386	178 (98.3)	12.691
Patients with any Grade ≥3 TEAE	241 (91.6)	1.171	152 (84.0)	0.986
Patients with any Grade 5 TEAE	29 (11.0)	0.031	10 (5.5)	0.019
Patients with any TEAE leading to definitive treatment discontinuation	60 (22.8)	0.066	47 (26.0)	0.090
Serious TEAEs		0.37		0.43

IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; TEAE=treatment-emergent adverse event; VRd=bortezomib+lenalidomide+dexamethasone
Source: CS, Table 37

Grade ≥3 haematologic laboratory abnormalities, adverse events and second primary cancers

A summary of the Grade ≥3 haematologic laboratory abnormalities, adverse events and second primary cancers reported in patients in the IMROZ trial is presented in Table 10. The EAG highlights that there are higher rates in the IsaVRd arm compared with the VRd arm of lymphopenia (60.1% versus 53%), neutropenia (54.4% versus 37%), leukopenia (31.6% versus 16.6%), pneumonia (20.2% versus 12.7%) and solid tumours (5.3% versus 3.3%).

Table 10 IMROZ trial grade ≥3 haematologic laboratory abnormalities, adverse events and second primary cancers

	IsaVRd (N=263)	VRd (N=181)
	Grade ≥3 n (%)	Grade ≥3 n (%)
Haematologic laboratory abnormalities		
Anaemia	46 (17.5)	29 (16.0)
Lymphopenia	158 (60.1)	96 (53.0)
Neutropenia	143 (54.4)	67 (37.0)
Leukopenia	83 (31.6)	30 (16.6)
Thrombocytopenia	79 (30.0)	50 (27.6)
Nonhaematologic adverse events		
Infection	118 (44.9)	69 (38.1)
Pneumonia	53 (20.2)	23 (12.7)
Bronchitis	7 (2.7)	3 (1.7)
Upper respiratory tract infection	2 (0.8)	2 (1.1)
Diarrhoea	20 (7.6)	15 (8.3)
Peripheral sensory neuropathy	19 (7.2)	11 (6.1)
Cataract	41 (15.6)	20 (11.0)
Constipation	6 (2.3)	3 (1.7)
Fatigue	21 (8.0)	12 (6.6)
Peripheral oedema	0	2 (1.1)
Infusion-related reaction	1 (0.4)	0
Covid-19	23 (8.7)	12 (6.6)
Insomnia	10 (3.8)	4 (2.2)
Back pain	9 (3.4)	3 (1.7)
Asthenia	7 (2.7)	4 (2.2)
Invasive second primary cancer		
Solid tumour	14 (5.3)	6 (3.3)
Haematologic cancer	1 (0.4)	2 (1.1)

IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; VRd=bortezomib+lenalidomide+dexamethasone
Source: CS, Table 38

3.6.1 EAG conclusions: safety and tolerability

The company states (CS, p104) that the IsaVRd treatment regimen was associated with the known and manageable tolerability profile of the components of the regimen. Clinical advice to the EAG is that no unexpected safety concerns associated with the use of IsaVRd arose during the IMROZ trial.

3.7 EAG summary and critique of the indirect comparisons

In the absence of direct clinical effectiveness evidence for the comparison of IsaVRd versus DRd, Rd, VCd and VMP, the company caried out ITCs. The company carried out a SLR (CS, Appendix D.1) and a feasibility assessment (Appendix D.3). Initially the company performed a network meta-analysis (NMA). However, to form a connected network, it was necessary to include non-randomised SWG S0777[17,18] trial subgroup data as a proxy for the transplant ineligible population data and this approach introduced bias due to:

- data from patients aged ≥65 years being used as a proxy for transplant ineligible patients
- imbalances between treatment arms due to randomisation not being preserved
- bortezomib administered IV causing neuropathy which resulted in 23% of patients prematurely discontinuing VRd induction treatment and, therefore, possible confounding.

The company carried out NMAs (using methods that were consistent with guidance published in NICE Decision Support Unit [DSU] Technical Support Document [TSD] 18.[19] However, the company considered that these NMA results were not robust and carried out unanchored OS and PFS MAICs to generate clinical effectiveness data for the comparison of IsaVRd versus DRd, Rd and VMP. For information, NMA input data are presented in CS, Appendix D.3.1.5, NMA methods are presented in CS, 3.1.6 and NMA results are presented in CS, Appendix D.3.1.7. Company constant HR MAIC methods are available in CS, Appendix D.3.2.1, results are presented in the main body of the CS (CS, Section B.2.9.4) and the studies that provided data to inform the MAICs are listed in Table 11.

The company's two SLRs (i. RCTs and ii. non-RCTs and observational studies) did not identify any studies to support an ITC to compare the clinical effectiveness of IsaVRd versus VCd. The company considered two alternative VCd data sources, namely, i) UK National Cancer Registration and Analysis Service (NCRAS[20]) (UK data) and ii) Flatiron Health Multiple Myeloma Enhanced DataMart (US data).[21] The company rejected using NCRAS data due to the absence of individual patient data (IPD) and clinical advice that these data were heterogeneous (CS, p83). IPD were available from the Flatiron database and the company used IMROZ trial IPD and Flatiron IPD[22] to conduct inverse probability weighting (IPW).

Table 11 MAIC and IPW data sources

Treatment	Studies providing data for the company MAICs	Study design	OS data	PFS data
IsaVRd	IMROZ trial	Phase III, multicentre, international, open-label RCT	Individual patient-data	Individual patient-data
Unanchored MAIC				
DRd	MAIA trial	Phase III, multicentre, international, open-label RCT	TA917[23]	Kumar et al. 2022[24]
Rd	MAIA trial	Phase III, multicentre, international, open-label RCT	TA917[23]	Kumar et al. 2022[24]
	FIRST trial	Phase III, multicentre, international, open-label RCT	Facon et al. 2018[25]	Facon et al. 2018[25]
VMP	ALCYONE trial	Phase III, multicentre, international, open-label RCT	Mateos et al. 2022[26]	Mateos et al. 2022[26]
IPW				
VCd	Flatiron database	US retrospective cohort study	Individual patient-data[22]	Individual patient-data[22]

DRd=daratumumab+lenalidomide+dexamethasone; IPW=inverse probability weighting; IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; MAIC=matching adjusted indirect comparison; OS=overall survival; PFS=progression-free survival; RCT=randomised controlled trial; Rd=lenalidomide+dexamethasone; VCd=bortezomib+cyclophosphamide+dexamethasone; VMP=bortezomib+melphalan+prednisone
Source: CS, Table 23

3.7.1 Quality assessment of included studies

The company assessed the quality of the 76 trials using the minimum criteria recommended by NICE.[12] The company quality assessment results are provided as part of the company submission (CS, Section B.2.5 [IMROZ trial] and Appendix D.1.1.2.2 [MAIA, FIRST and ALCYONE trials]).

The only area of concern relating to the four RCTs[11,27-29] that provided data for the company MAICs was that all the trials were open-label trials, i.e., providers, participants and outcome assessors were not blind to treatment allocation. However, all four trials provided independent review committee PFS data and these data were used to inform the MAICs. The EAG agrees with the company's quality assessment results.

3.8 EAG critique of company ITC methods

3.8.1 EAG critique of company NMA methods

The EAG considers that the company approach to NMAs was appropriate and the NMA is unlikely to have been affected by cross-over (company response to clarification question A7). However, the EAG agrees with the company that NMA results are unlikely to be robust as it was necessary to include non-randomised SWOG S0777[18] trial subgroup data as a proxy for transplant ineligible population data (see Section 3.7). The EAG highlights that OS NMA results presented in the CS have been (incorrectly) derived from the global network rather than the smaller network of comparators relevant to this appraisal; these results are presented in CS, Appendix D, Table 29.

3.8.2 EAG critique of company constant HR MAIC methods

The company conducted MAICs to generate clinical effectiveness data for the comparison of IsaVRd versus DRd, Rd and VMP.

MAICs: constant hazards approach

The EAG considers that the company MAIC was implemented appropriately (i.e., consistent with guidance published in NICE DSU TSD 18[19]).

However, the EAG notes that the company's estimates of comparative efficacy are based on unanchored comparisons; these comparisons rely on strong assumptions that are difficult to satisfy, including the assumption that all potential prognostic factors and treatment effect modifiers are accounted for and included in the model (i.e., there are no unobserved prognostic factors or effect modifiers). The company identified nine potential prognostic factors/treatment effect modifiers, namely: frailty, age, International Staging System stage, cytogenetic risk, chromosomal abnormality 1q21+, ECOG PS, LDH levels, creatinine clearance, and MM type IgG. The EAG agrees with the approach taken by the company to identify these prognostic factors/treatment effect modifiers, namely consultation with clinicians and univariate analyses of IMROZ trial IPD. It was not possible to adjust for three of the identified prognostic factors/treatment effect modifiers, namely frailty, chromosomal abnormality 1q21+ and LDH levels. The EAG considers that as only six factors were adjusted for in the matching process, this could potentially introduce bias due to unmeasured confounding; clinical advice to the EAG is that the extent of any bias is unknown but is anticipated to be minimal.

The EAG agrees with the company that, after weighting, average baseline characteristics (mean or proportion of patients within a category) were balanced for the IsaVRd-treated

patients and the comparator-treated patients; this indicates that weights were estimated correctly. Further, ESS were reasonable (56 to 62% of original sample size) and histograms showed no extreme values.

PFS, OS and TTD MAIC HRs (95% CI) were generated using unadjusted Cox model, weighted Cox PH regression model, and bootstrapping with percentile CI. The Cox PH model is only appropriate when there is no violation of the PH assumption. The company explained (company response to clarification question A9) that although no Schoenfeld global test results were statistically significantly different (i.e., p-value<0.05), for most comparisons there was some evidence that the PH assumption did not hold, for example non-parallel and/or crossing of log-cumulative hazard curves and/or curved smoothed Schoenfeld residual plots lines. The EAG has examined all the PH data provided by the company and considers that, on balance, it is reasonable to assume that the PH assumption holds for all comparisons.

MAICs: time varying approach

The EAG considers that the company approach to carrying out time-varying MAICs was reasonable, and methods appear to have been implemented correctly. In response to clarification question A9, the company explained that it was necessary to adopt a time varying approach due to uncertainty around whether the PH assumption was valid for all time to event outcomes for all comparisons; the EAG considers that, on balance, for all comparisons, there is insufficient evidence to reject the PH assumption. The EAG highlights that time varying MAIC HRs were used in the company's base case economic analyses. These results were presented in the CS (CS, Table 51 and Table 55). Additional details, including landmark HRs and figures illustrating time-varying HRs over time for all distributions, are presented in the CS (CS, Appendix I, Tables 98-105 and Figures 80-87). Company base case cost effectiveness scenario analysis results generated using constant HR MAICs (and list prices) do not affect the interpretation of company base case results.

3.8.3 EAG critique of company IPW methods

IPW methods were used by the company to generate comparative clinical effectiveness results for the comparison of IsaVRd versus VCd due to the availability of IMROZ trial and Flatiron database IPD.

In response to clarification question A11, the company confirmed that, rather than carry out propensity score matching, the IPW approach was selected as in order to utilise all available data whereas propensity score matching reduces the sample size by discarding unmatched data. The EAG considers that it was appropriate to use the IPW method and suggests that

scenario analysis results from propensity score matching or regression adjustment would have been useful to explore uncertainty around the estimates of comparative efficacy.

Propensity scores for IMROZ trial IsaVRd patients versus Flatiron VCd patients were derived using logistic regression (known as the propensity score model). The final propensity score model adjusted for the following covariates: age, ECOG PS, International Staging System Stage, time from MM diagnosis to treatment, cytogenetic risk, and chromosomal abnormality 1q21+. Two of these factors differ from the factors adjusted for in the company MAICs (included in the MAICs only: MM type Ig; included in the IPW only: time from MM diagnosis, chromosomal abnormality 1q21+). The EAG considers that as only six factors were adjusted for, this could potentially introduce bias due to unmeasured confounding; clinical advice to the EAG is that the extent of any bias is unknown.

Following estimation of the propensity scores, statistical weights were derived using the average treatment effect for the treated (ATT) estimand (i.e., IMROZ as the target population). The EAG considers that the approach taken by the company to trim weights was appropriate. The ATT estimand was based on re-weighting the Flatiron VCd population so that it was similar to the IMROZ population in terms of the prognostic factors and treatment effect modifiers adjusted for in the model. The EAG highlights that only a small number of Flatiron patients were assigned large weights (assigned to the 99th percentile) and only one patient was assigned an extreme weight (no information was provided to explain this extreme weight). Of note, the company's IPW approach re-weighted Flatiron data to match IMROZ trial data whilst the company's MAIC approach matched IMROZ trial population data to the relevant comparator trial population data. The EAG considers that this approach was appropriate from a statistical perspective.

3.8.4 Company ITC results

Table 12 Company progression-free survival hazard ratios: IsaVRd versus each comparator

	Unanchored MAIC	IPW
	PFS HR (95% CI)	
DRd	[redacted]	-
VMP	0.20 (0.15 to 0.27)	-
Rd	[redacted]	-
VCd	-	0.34 (0.25 to 0.47)

CI=confidence interval; DRd=daratumumab+lenalidomide+dexamethasone; HR=hazard ratio; IPW=inverse probability weighting; MAIC=matching adjusted indirect comparison; Rd=lenalidomide+dexamethasone; VCd=bortezomib+cyclophosphamide+dexamethasone; VMP=bortezomib+melphalan+prednisone
Source: CS, Table 24, Table 27, Table 29, Table 31

Table 13 Company overall survival hazard ratios: IsaVRd versus each comparator

	Unanchored MAIC	IPW
	OS HR (95% CI)	
DRd	[redacted]	-
VMP	0.50 (0.37 to 0.67)	-
Rd	[redacted]	-
VCd	-	0.48 (0.33 to 0.69)

CI=confidence interval; DRd=daratumumab+lenalidomide+dexamethasone; HR=hazard ratio; IPW=inverse probability weighting; MAIC=matching adjusted indirect comparison; Rd=lenalidomide+dexamethasone; VCD=bortezomib+cyclophosphamide+dexamethasone; VMP=bortezomib+melphalan+prednisone
Source: CS, Table 25, Table 28, Table 30, Table 32

3.9 Conclusions of the clinical effectiveness section

The main source of IsaVRd clinical effectiveness evidence is the IMROZ trial. The IMROZ trial is an ongoing, international phase III, open-label, RCT that compares the efficacy and safety of IsaVRd (n=265) with VRd (n=181) in patients with NDMM who are ineligible for ASCT. The trial population matches the patient population specified in the final scope[2] issued by NICE. The EAG considers that the IMROZ trial is of good methodological quality, however, the IMROZ trial data are immature; median PFS in the IsaVRd arm has not been reached and median OS has not been reached in either trial arm.

The comparator in the IMROZ trial, VRd, is not a relevant NHS comparator for this appraisal. The company carried out ITCs to generate evidence to compare the clinical effectiveness of IsaVRd with DRd, VMP, Rd and VCd and. Clinical advice to the EAG is that DRd is the main comparator.

The EAG considers that the company approach to generating ITC evidence to compare the clinical effectiveness of IsaVRd versus DRd, VMP and Rd was comprehensive. The EAG agrees with the company that MAIC results are likely to be more reliable than NMA results.

The EAG has no strong concerns relating to use of IPW to compare the clinical effectiveness of IsaVRd versus VCd.

The EAG highlights that none of the unanchored ITC approaches adopted by the company adjusted for all important prognostic factors/treatment effect modifiers and this could potentially introduce bias due to unmeasured confounding; clinical advice to the EAG is that the extent of any bias is unknown.

4 COST EFFECTIVENESS EVIDENCE

This section provides a summary of the economic evidence submitted by the company in support of the use of IsaVRd as a treatment option for adult patients with NDMM who are ineligible for ASCT. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft® Excel.

4.1 Company review of published cost effectiveness evidence

The company undertook a SLR to identify the characteristics and results of economic models developed to assess the cost effectiveness of treatments for NDMM.

The company literature search was conducted in January 2023 and updated in April 2024. Electronic databases were searched from 2020 to 2024. Health Technology Assessment (HTA) websites and databases, and bibliographies of relevant SLRs published since 2016 were searched to identify any publication that had not been identified by the electronic database search. Full details of the literature searches and results are reported in CS, Appendix G.

The company's SLR identified 56 publications relating to adults with NDMM; 27 economic evaluations were reported in journal publications and 29 were published HTA reports. The company considered that four studies of transplant ineligible patients were relevant, namely, three cost utility analyses that had been carried out to inform NICE Technology Appraisals[23,30,31] and one cost impact analysis[32] (setting: UK and four EU countries). The company assessed the quality of these four studies using the Drummond checklist[33] (see CS, Appendix G.3).

4.2 EAG critique of the company's economic model literature review

The EAG considers that the methods used by the company to identify the characteristics and results of published models were mostly of a good standard (Table 14). The combination of index terms and free-text words, used by the company to search electronic databases for relevant economic evaluations, pharmacological interventions, and disease (source for economic search filters not reported) was appropriate. However, the EAG highlights that when conducting a systematic review, searching MEDLINE and Embase simultaneously using a single strategy may be suboptimal, as these databases use different indexing terms, truncation symbols, and Boolean and proximity operators, which could lead to variations in search results. In this instance, however, this approach is not likely to have had a significant impact on search results.

The three included NICE Technology Appraisals[23,30,31] largely met the Drummond checklist[33] criteria; however, QALYs, costs and ICERs per QALY gained were not publicly available. Limited information was reported by Schey[32] and thus it was not possible to assess whether all the Drummond[33] criteria had been met in this cost impact analysis. Further, as the cost impact analysis was conducted from the perspective of multiple countries, the relevance to this NICE technology appraisal of IsaVRd is unclear.

Table 14 EAG appraisal of systematic review methods (cost effectiveness, HRQoL and healthcare resource use/cost)

Review process	EAG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Unclear; this information was not provided in response to clarification question C2
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Were data extracted by two or more reviewers independently?	Extracted by one reviewer and checked by a second reviewer
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Yes
Were attempts to synthesise evidence appropriate?	Not applicable

EAG=External Assessment Group; HRQoL=health-related quality of life; LR*i*G=Liverpool Reviews and Implementation
Source: LR*i*G in-house checklist

The company also carried out HRQoL (CS, Section B.3.4.3 and Appendix H) and resource use (CS, Section B.3.5.1 and Appendix I) literature reviews.

4.2.1 EAG concluding remarks

The economics search strategies and resources searched were generally appropriate and searches were replicable.

4.3 EAG summary and critique of the company's submitted economic evaluation

4.3.1 NICE Reference Case checklist and Drummond checklist

Table 15 NICE Reference Case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	The scope developed by NICE	✓
Comparators	As listed in the scope developed by NICE	✓
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	✓
Perspective on costs	NHS and PSS	✓
Type of economic evaluation	Cost utility analysis with fully incremental analysis	✓
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	✓
Synthesis of evidence on health effects	Based on systematic review	✓
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	✓
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	✓
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	✓
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✓
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	✓
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	✓

EAG=External Assessment Group; EQ-5D=EuroQol-5 dimensions; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; PSS=Personal Social Services; QALY=quality adjusted life year
Source: EAG assessment of NICE Reference Case[34]

Table 16 Critical appraisal checklist for the economic analysis completed by the EAG

Question	Critical appraisal	EAG comment
Was a well-defined question posed in answerable form?	✓	-
Was a comprehensive description of the competing alternatives given?	✓	-
Was the effectiveness of the programme or services established?	Partial	Median PFS has not been reached in the IMROZ trial IsaVRd arm and median OS has not been reached in either of the IMROZ trial arms
Were all the important and relevant costs and consequences for each alternative identified?	✓	-
Were costs and consequences measured accurately in appropriate physical units?	Partial	There is insufficient evidence to support the survival advantage, modelled by the company, for IsaVRd over DRd
Were the cost and consequences valued credibly?	Partial	The company post-progression survival utility values are too pessimistic
Were costs and consequences adjusted for differential timing?	✓	-
Was an incremental analysis of costs and consequences of alternatives performed?	✓	-
Was allowance made for uncertainty in the estimates of costs and consequences?	✓	-
Did the presentation and discussion of study results include all issues of concern to users?	✓	-

DRd=daratumumab+lenalidomide+dexamethasone; EAG=External Assessment Group; IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; OS=overall survival; PFS=progression-free survival
Source: Drummond and Jefferson[33]

4.4 Cost effectiveness data presented in the EAG report

All the data provided in Section 4.5 to Section 5.2 of this report relate to the company base case analysis (presented in the CS). The company provided additional cost effectiveness results (Scenario A: 60 months of IMROZ trial data; Scenario B: final MAIA trial DRd data) in response to the clarification letter.

4.5 Model structure

The company developed a de novo partitioned survival model in Microsoft® Excel. This structure is standard in oncology health technology assessment (HTA) submissions. The model comprises three mutually exclusive health states:

- progression-free (PF); this health state comprises two sub-health states: on-treatment and off-treatment
- post-progression (PP)
- death

An illustration of the model structure is presented in Figure 2. The proportion of patients occupying each health state is estimated using PFS and OS curves (see Section 4.9). The OS rate is capped by the age- and gender-matched general population mortality rate. All patients are assumed to be dead at 100 years old. In each cycle, the PFS rate is capped by the OS rate to ensure that OS is never greater than PFS.

In the PF health state, patients incur the cost (acquisition and administration) of the intervention or comparator, monitoring costs and AE management costs; PF- and AE-associated utilities are applied. In the PP health-state, patients incur monitoring and subsequent treatment costs; PP utilities are applied. Patients who transition to the death health state incur a one-off end-of-life cost. Costs and QALYs are accumulated over the model time horizon and total costs and total QALYs are used to estimate ICERs per QALY gained (IsaVRd versus each comparator).

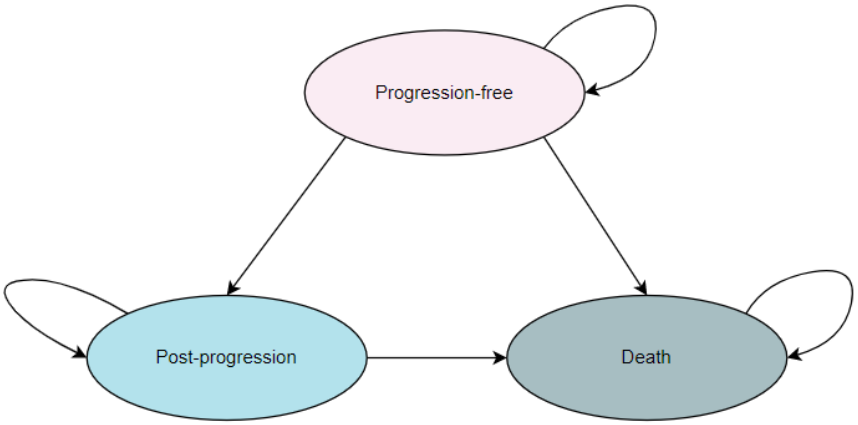


Figure 2 Structure of the company model

Source: CS, Figure 32

4.6 Population

In line with the proposed IsaVRd licence and the IMROZ trial population, the population entering the model was adult patients with TI-NDMM. The model baseline patient characteristics (Table 17) reflect the baseline characteristics of the IMROZ trial [redacted] population (n=446).

Table 17 Model population characteristics

Baseline characteristic	IMROZ trial ITT population
Age at the start of the model	71.63 years
Proportion male	53%
Weight	73.58kg
Body surface area	1.8m^2
Proportion with regular renal function	70.9%
Proportion with moderate renal impairment	29.1%

ITT=intention-to-treat
Source: CS, Table 44

4.7 Interventions and comparators

4.7.1 Intervention

The modelled intervention was IsaVRd. In line with the IMROZ trial protocol, treatment was delivered in two phases:

- induction phase: IsaVRd for 24 weeks
- continuous treatment: IsaRD until disease progression, unacceptable AEs or the patient's decision to discontinue.

Patients with moderate renal impairment (creatinine clearance between 30 and 60mL/min) received a reduced dose of lenalidomide.

Isatuximab was delivered via IV infusion. Dexamethasone may be delivered via IV infusion or orally. Lenalidomide is an oral drug and bortezomib is delivered via SC injection.

4.7.2 Comparators

In line with the final scope[2] issued by NICE, the company has considered the following comparators: DRd, VMP, Rd, and VCd. In the company model, DRd, Rd and VMP were implemented in line with their respective marketing authorisations,[8,9,35] and dosing schedules were in line with each drug's summary of product characteristics (SmPCs) or relevant trial protocols.[8,9,35] There was no relevant VCd trial and therefore, in the model, VCd was administered in line with NHS dosing protocols.[36] The company has assumed that all patients receive daratumumab via SC injection (daratumumab may also be delivered via IV infusion).

The dosing schedules for the intervention and comparators are presented in CS, Table 46.

4.8 Perspective, time horizon and discounting

The model perspective was reported as NHS and Personal Social Services (PSS). The model cycle length was 2 weeks (14 days). The model time horizon (29 years) was set based on the assumption that all patients will die by the age of 100 years. Costs and outcomes were discounted at a rate of 3.5% per annum.

4.9 Treatment effectiveness and extrapolation

4.9.1 Parametric distribution selection: IsaVRd

The process used by the company to select parametric distributions to extrapolate IMROZ trial IsaVRd OS, PFS, and TTD data was in line with the process described in NICE TSD 14.[37] In brief:

- seven standard parametric distributions (exponential, gamma, generalised gamma, Gompertz, log-logistic, log-normal and Weibull) were fitted to IMROZ trial IsaVRd Kaplan-Meier (K-M) data
- Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) scores were used to assess goodness of fit
- The visual goodness of fit of the seven parametric distributions to the IMROZ trial data was assessed by comparing IMROZ trial IsaVRd smoothed hazards with the hazard profiles of the seven parametric distributions
- clinical plausibility was determined by comparing company clinical expert 5, 10, 15 and 20 year survival estimates with the survival rates generated by the seven parametric distributions

Information about the parametric distributions used in the company base case analyses and a summary of the company rationale for choosing these distributions are presented in Table 18.

Table 18 Distributions used in the company base case analyses to extrapolate IMROZ trial IsaVRd OS, PFS and TTD data

Endpoint	Curve selection	Company brief rationale
PFS	Weibull	The gamma, Gompertz and Weibull distributions provided the most plausible estimates; the Gamma distribution was chosen due to having the best statistical fit
OS	Gompertz	Generalised gamma and Gompertz distributions provided the most plausible estimates; however, the statistical fit of the Gompertz distribution was better than that of the generalised gamma distribution
TTD	Exponential	Best statistical fit

OS=overall survival; PFS=progression-free survival; TTD=time to treatment discontinuation
Source: CS, Section B.3.3

4.9.2 Effectiveness of comparator treatments

OS and PFS: DRd, Rd, VCd and VMP

In the absence of head-to-head trials, and as the company considered that there was uncertainty around whether the PH assumption was valid for comparisons between IsaVRd and any comparator treatment, time-varying HRs were used in the company base case analysis to generate OS and PFS estimates; these time-varying HRs were anchored to the IsaVRd OS, PFS and TTD parametric distributions. For OS only and for the period from the end of the IMROZ trial follow-up to the end of the model time horizon, the HR was fixed. As

there was an improving relative treatment effect for the comparison of IsaVRd OS versus all comparators and, the company considered that this approach was conservative. Landmark PFS and OS HRs are displayed in Table 19 and Table 20 respectively.

Table 19 Landmark progression-free survival hazard ratios

Time (years)	HR (95% CI) for IsaVRd (gamma distribution) versus comparators			
	DRd	Rd	VMP	VCd
1	[redacted]	[redacted]	0.21 (0.15 to 0.29)	0.35 (0.25 to 0.47)
2	[redacted]	[redacted]	0.18 (0.13 to 0.26)	0.33 (0.24 to 0.45)
5	[redacted]	[redacted]	0.16 (0.11 to 0.26)	0.32 (0.21 to 0.48)
5.67*	[redacted]	[redacted]	0.16 (0.11 to 0.26)	0.32 (0.21 to 0.48)
10	[redacted]	[redacted]	0.15 (0.10 to 0.26)	0.31 (0.20 to 0.50)
28	[redacted]	[redacted]	0.14 (0.08 to 0.27)	0.31 (0.18 to 0.52)

CI=confidence interval; HR=hazard ratio; DRd=daratumumab+lenalidomide+dexamethasone; IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; Rd=lenalidomide+dexamethasone; VCd=bortezomib+cyclophosphamide+dexamethasone; VMP=bortezomib+melphalan+dexamethasone
* End of IMROZ trial follow-up
Source: CS, Table 56

Table 20 Landmark overall survival hazard ratios

Time (years)	HR (95% CI) for IsaVRd (Gompertz distribution) versus comparators			
	DRd	Rd	VMP	VCd
1	[redacted]	[redacted]	0.66 (0.43 to 1.01)	0.51 (0.32 to 0.82)
2	[redacted]	[redacted]	0.56 (0.40 to 0.78)	0.47 (0.32 to 0.68)
5	[redacted]	[redacted]	0.34 (0.17 to 0.66)	0.36 (0.20 to 0.62)
5.67*	[redacted]	[redacted]	0.30 (0.13 to 0.67)	0.33 (0.17 to 0.65)
10	[redacted]	[redacted]	0.15 (0.03 to 0.79)	0.22 (0.06 to 0.94)
28	[redacted]	[redacted]	0.01 (0.00 to 1.94)	0.04 (0.00 to 5.32)

CI=confidence interval; HR=hazard ratio
* End of IMROZ trial follow-up
CI=confidence interval; HR=hazard ratio; DRd=daratumumab+lenalidomide+dexamethasone; IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; Rd=lenalidomide+dexamethasone; VCd=bortezomib+cyclophosphamide+dexamethasone; VMP=bortezomib+melphalan+dexamethasone
Source: CS, Table 51

TTD: DRd

The company considered that, based on the HR for the comparison of IsaVRd versus DRd TTD (HR: [redacted]), it was appropriate to apply the point estimate HR from this analysis to the IsaVRd TTD distribution to generate TTD data for patients treated with DRd.

TTD: Rd, VMP and VCd

TTD data for Rd, VCd and VMP were not publicly available. The company, therefore, assumed that median duration of treatment (DoT) could be considered a proxy for median TTD. For each comparator treatment, the company derived a HR between median PFS and median DoT and applied the result to the comparator PFS curve. Treatment stopping rules were

applied to TTD for patients treated with VCd[36] (at 24 weeks) and patients treated with VMP[8] (at 54 weeks).

4.9.3 General population mortality

To ensure that OS never exceeded that of the general population, the company applied age- and gender-matched general population mortality[38] in any cycle where the predicted rate of death was lower than the general population mortality rate. National Statistics 2017-2019 life tables for England[38] data were used as more recent data potentially incorporate biases due to COVID-19 (this approach is in line with TSD 23[39] guidance).

4.9.4 Adverse events

Grade ≥3 AEs that occurred in at least 5% of patients were included in the company model; this resulted in 19 AEs being identified. The ten Grade ≥3 AEs that occurred in at least 10% of patients are presented in (Table 21).

Table 21 Incidence of Grade ≥3 AE reported (≥10% of patients for one comparator)

Adverse event	IsaVRd	DRd	Rd	VMP	VCd
Source	IMROZ CSR[13] (Table 57)	Facon 2021[40] (MAIA, DRd)	Facon 2021[40]	San Miguel[41] (VISTA)	Assumed equal to VMP
Number of patients	263	364	365	340	340
Neutropenia	79 (30.0%)	197 (54.1%)	135 (37.0%)	136 (40.0%)	136 (40.0%)
Anaemia	0 (0.0%)	61 (16.8%)	79 (21.6%)	62 (18.2%)	62 (18.2%)
Lymphopenia	0 (0.0%)	60 (16.5%)	41 (11.2%)	67 (19.7%)	67 (19.7%)
Leukopenia	0 (0.0%)	42 (11.5%)	23 (6.3%)	77 (22.7%)	77 (22.7%)
Thrombocytopenia	31 (11.8%)	32 (8.8%)	34 (9.3%)	126 (37.1%)	126 (37.1%)
Pneumonia	53 (20.2%)	70 (19.2%)	39 (10.7%)	22 (6.5%)	22 (6.5%)
Hypokalaemia	0 (0.0%)	46 (12.6%)	36 (9.9%)	22 (6.5%)	22 (6.5%)
Cataract	41 (15.6%)	40 (11.0%)	39 (10.9%)	0 (0.0%)	0 (0.0%)
Peripheral sensory neuropathy	19 (7.2%)	0 (0.0%)	0 (0.0%)	44 (12.9%)	44 (12.9%)

CSR=clinical study report; DRd=daratumumab+lenalidomide+dexamethasone; IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; Rd=lenalidomide+dexamethasone; VCd=bortezomib+cyclophosphamide+dexamethasone; VMP=bortezomib+melphalan+dexamethasone
Source: CS, Table 59

4.10 Health-related quality of life

Health state utility values were derived from IMROZ trial EQ-5D-5L data mapped to EQ-5D-3L data using the Hernandez Alava[42] mapping algorithm. Values were generated using three regression models:

- Model 1: model using stepwise selection (parameters: baseline utility, age, sex, progression status, ECOG PS, treatment, OR, sex/treatment, ECOG PS/treatment and OR/treatment)

- Model 2: as Model 1 excluding OR
- Model 3: Model 1 excluding OR and treatment/treatment combinations.

In the company base case analysis, the PF health state utility value for patients treated with IsaVRd was generated using Model 2 (investigator-assessed PFS, without OR and with a treatment effect due to the statistically significant improvement in utility for patients treated with IsaVRd compared with those treated with VRd). The company considered that it was not appropriate to use PPS utility values generated using IMROZ trial data as 79.8% (217/272) post-progression survival records were collected within 6 months of the progression event. Therefore, in the base case, the PPS utility was sourced from TA587.[31]

For comparator treatments, the DRd PFS utility value was assumed to be the same as the IsaVRd utility value (both are anti-CD38 agents). Rd, VMP and VCd PFS utility values were assumed to be the same as the IMROZ trial VRd utility value (Model 2, without OR).

Company base case utility values are presented in Table 22.

Table 22 Progression-free and post-progression survival health state utility values

Health state	IsaVRd	DRd	Rd	VMP	VCd	Source
PFS	0.728	0.728	0.688	0.688	0.688	IMROZ trial
PPS	0.557	0.557	0.557	0.557	0.557	TA587[31]

PFS=progression-free survival; PPS=post-progression survival
DRd=daratumumab+lenalidomide+dexamethasone; IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; Rd=lenalidomide+dexamethasone; VCd=bortezomib+cyclophosphamide+dexamethasone; VMP=bortezomib+melphalan+dexamethasone
Source: CS, Table 64

4.10.1 Adverse event disutilities

The impact of treatment-related AEs on HRQoL was implemented as a one-off QALY loss for each AE; disutilities were deducted from patients' pre-progression health state utility. Event duration and utility decrements were sourced from TA917[23] for all AEs except peripheral sensory neuropathy (source: TA870[43]), syncope (source: TA970[44]) and COVID-19 pneumonia (assumed equal to the disutility associated with pneumonia). The AE disutilities used in the company model ranged from -0.153 (anaemia) to 0.000 (syncope). The AE disutilities included in the company model are presented in CS, Table 61.

4.11 Resource use and costs

4.11.1 Drug costs

Unit costs

Drug costs for brand-name treatments were sourced from the Monthly Index of Medical Specialities (MIMS). Costs of drugs available as generics were sourced from the electronic Market Information Tool (eMIT) or the British National Formulary (BNF). All costs were sourced from 2023/24 releases.

Acquisition costs were calculated per administration and were estimated based on each drug's respective dosing schedule.[45-47] Details are provided in CS, Appendix I.7.

In the company model, relative does intensity (RDI) multipliers (CS, Appendix I, Table 107) were used to estimate drug costs. The sources of these RDIs are presented in Table 23.

Table 23 Sources of relative dose intensity multipliers used in the company model

Drug	Source
IsaVRd	IMROZ trial
DRd*	MAIA trial[28]
Rd	MAIA trial[28]
VMP	ALCYONE trial[27]
VCd	Assumed equal to VMP

* RDI for daratumumab was assumed equal when administered via subcutaneous injection (in line with TA917[23] assumption)
RDI=relative dose intensity
DRd=daratumumab+lenalidomide+dexamethasone; IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; Rd=lenalidomide+dexamethasone; VCd=bortezomib+cyclophosphamide+dexamethasone; VMP=bortezomib+melphalan+dexamethasone
Source: CS, Section 3.5.2.1

For drug doses that were based on weight or body surface area (BSA), the 'method of moments' was applied to estimate average dose accounting for wastage (no vial sharing). IMROZ trial data were used as the source of patient weight and BSA distributions. It was assumed that there was no wastage for oral drugs.

Lenalidomide is prescribed based on the patient's renal function. In the company model, using IMROZ trial data (CS, Table 44), the costs of the 25mg and 10mg doses were weighted by the proportion of patients with regular (70.9%) and moderately impaired (29.1%) renal function.

Dexamethasone dosing for patients aged <75 years receiving IsaVRd was applied to the whole time horizon and did not reduce once patients reached the age of 75 years. The company considered that this assumption was conservative and had a minimal impact on cost effectiveness results due to the low cost of dexamethasone.

Drug administration costs

Drug administration costs were sourced from NHS Reference Costs 2022-23.[48] Following advice from an NHS pharmacist (during TA658[49]), only the highest administration cost associated with any component of a combination treatment was applied. In line with TA917,[23] the company assumed that all patients would receive SC daratumumab.

The drug administration costs used in the company model are presented in Table 24.

Table 24 Drug administration method and cost per administration

Administration type	Cost per administration	Source: NHS Reference Costs 2022–23[48]
IV - first dose	£486.10	Total HRG: SB13Z – Deliver more complex parenteral chemotherapy at first attendance
IV - prolonged first dose	£544.86	SB14Z - Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance
IV - subsequent dose	£393.16	Total HRG: SB15Z – Deliver subsequent elements of a chemotherapy cycle
SC - first and subsequent doses	£411.99	Total HRG: SB12Z – Deliver simple parenteral chemotherapy at first attendance
Oral - first dose	£322.00	Total HRG: SB11Z – Deliver exclusively oral chemotherapy
Oral - subsequent dose	0.00	Assumption

HRG=healthcare resource group; IV=intravenous; SC=subcutaneous
Source: CS, Table 66

Concomitant treatment costs

The concomitant treatments included in the company model were those specified in the treatment[7] and comparator[8,35] SmPCs, namely paracetamol, H2 blocker (cimetidine) diphenhydramine, methylprednisolone and aciclovir. The highest dose of each pre-medication regimen was included in the model. It was assumed that the daratumumab concomitant treatments (required pre- and post-daratumumab administration) were applied at the same time as the daratumumab administration. List prices (eMIT[47] and MIMS[46]) were used to generate costs. The costs of concomitant treatments per administration are provided in Table 25.

Table 25 Concomitant treatment cost per administration

Treatment requiring concomitant medication	Cost per administration
Isatuximab (IMROZ[11] protocol)	£8.03[46,47]
Daratumumab (Darzalex SmpC[35])	£4.66[46,47]
Bortezomib (Velcade SmPC[8])	£0.01[47]

SmPC= Summary of Product Characteristics
Source: CS, Table 69

Subsequent treatments

Subsequent treatments were only modelled to affect costs. Ten clinical experts provided information to reflect the distribution of subsequent treatments currently used in NHS clinical practice in the second-, third- and fourth-line settings. Attrition rates between first-line treatment and second-line treatment were derived from the pivotal trials of each first-line treatment, and the attrition rates between all other lines of treatment were derived from Yong.[50]

Subsequent treatment durations in the second-line and third-line settings were sourced from TA917;[23] treatment duration in the fourth-line setting was sourced from TA763[51] (not reported in TA917[23]). Where treatment durations were not included in TA763,[51] they were assumed equal to pomalidomide and dexamethasone (Pd) duration as Pd is the minimum effective treatment given to patients in the fourth-line setting.

Treatment durations were multiplied by subsequent treatment distributions to generate a total cost of subsequent treatment over all lines of treatment. This cost was then imputed over the time horizon after disease progression or treatment discontinuation. Total costs of subsequent treatments (based on subsequent treatment distributions, drug costs, administration costs and subsequent treatment durations) are presented in Table 26.

Table 26 Subsequent treatment costs

Treatment line	IsaVRd	DRd	Rd	VCd	VMP
Acquisition costs					
Second-line subsequent treatment cost	[redacted]	[redacted]	**£97,819**	**£72,670**	**£81,311**
Third-line subsequent treatment cost	[redacted]	[redacted]	£12,334	£40,144	£53,028
Fourth-line subsequent treatment cost	[redacted]	[redacted]	£7,295	£7,345	£7,384
Total acquisition costs	[redacted]	[redacted]	£117,448	£120,158	£141,722
Administration costs					
Second-line subsequent treatment cost	**£11,995**	**£15,442**	**£19,818**	**£15,960**	**£17,063**
Third-line subsequent treatment cost	£1,546	£2,794	£3,213	£853	£532
Fourth-line subsequent treatment cost	£340	£451	£592	£396	£233
Total administration costs	£13,881	£18,687	£23,623	£17,210	£17,828
Overall costs					
Total	[redacted]	[redacted]	**£141,071**	**£137,369**	**£159,549**

DRd=daratumumab+lenalidomide+dexamethasone; IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; Rd=lenalidomide+dexamethasone; VCd=bortezomib+cyclophosphamide+dexamethasone; VMP=bortezomib+melphalan+dexamethasone
Source: CS, Table 78

4.11.2 Health state costs and resource use

Monitoring costs

Modelled monitoring costs differed depending on whether patients were on- or off-treatment. On-treatment costs were applied to all patients in the PPS health state to account for the fact

that patients were treated with subsequent treatments until death. Medical resource use frequencies were identical across all treatment arms; this aligns with previous HTA submissions to NICE (TA917,[23] TA897[52] and TA763[51]). Costs were sourced from NHS Reference Costs 2022-23.[48] Monitoring frequencies and costs are presented in Table 27.

Table 27 Total health state resource use costs used in the company model

Item	On-treatment		Off-treatment		Source
	Frequency per 28 days	Frequency per cycle	Frequency per 28 days	Frequency per cycle	
Haematologist visit	0.92	0.23	0.32	0.08	Assumed to be equal to that reported in TA917,[23] and equal across all regimens
Full blood count	0.84	0.21	2.56	0.64	
Biochemistry	0.76	0.19	1.32	0.33	
Protein electrophoresis	0.52	0.13	0.72	0.18	
Immunoglobin	0.48	0.12	0.76	0.19	
Urinary light chain excretion	0.2	0.05	0.2	0.05	
Total cost	**£190.35**	**£95.18**	**£86.49**	**£43.24**	

TA=Technology Assessment
Source: CS, Table 71

4.11.3 Adverse events costs

In the company model, AE costs were applied as a one-off lump sum cost during the first model cycle. AE unit costs were sourced from NHS Reference Costs 2022-23[48] and align with the costs used to inform the NICE appraisal of DRd (TA917[23]). Total AE costs for each modelled treatment are presented in Table 28.

Table 28 Total AE costs for each modelled treatment

	IsaVRd	DRd	Rd	VCd	VMP
One-off cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse event
Source: company model

4.11.4 End-of-life costs

The company applied a one-off terminal care cost to the proportion of patients who died in each model cycle. The end-of-life cost was £13,314. This cost, sourced from Unit Costs of Health and Social Care 2023,[53] represents the cost of hospital and social care services for a cancer population, per decedent, in the final year of life.

4.11.5 Severity modifier

The company concluded that, based on results from the Schneider[54] QALY shortfall calculator, IsaVRd as a treatment option for patients with TI-NDMM, does not meet the NICE criteria for a QALY modifier.

5 COST EFFECTIVENESS RESULTS

Two sets of cost effectiveness results are presented in the CS, namely (i) those generated using list prices for all drugs and (ii) those generated using PAS discounts known to the company, or confidential discounts assumed by the company (carfilzomib, daratumumab, ixazomib, panobinostat, pomalidomide, thalidomide).

The company base case pairwise deterministic and probabilistic results for the comparison of IsaVRd versus DRd, using list prices, are presented in Table 29. The company has presented a full set of cost effectiveness results in CS, Appendix J.

Table 29 Company base case deterministic and probabilistic results (list prices for all drugs)

Treatment	Total		Incremental		ICER (£/QALY)	NHB*	Incremental NHB
	Costs	QALYs	Costs	QALYs			
Deterministic results							
DRd	[redacted]	[redacted]	-	-	-	[redacted]	
IsaVRd	[redacted]	[redacted]	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]
Probabilistic results							
DRd	[redacted]	[redacted]	-	-	-	[redacted]	
IsaVRd	[redacted]	[redacted]	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]

* Estimated using a threshold of £30,00
DRd=daratumumab+lenalidomide+dexamethasone; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; NHB=net health benefit; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: CS, Table 81 and Table 84 and EAG calculation

The EAG highlights that cost effectiveness results for Scenario A and Scenario B are presented in the company clarification response.

5.1 Deterministic sensitivity analyses

The company varied individual parameter input values. The parameter inputs were varied by upper and lower 95% CIs or, if not available, a 10% standard error (SE) was assumed to inform the 95% CI. Beta distributions (bound by 0 and 1) were assumed for utilities, proportions and probabilities, log-normal distributions were assumed for HRs, and gamma distributions were assumed for other uncertain parameters (including cost parameters). The parameters that had the biggest impact on ICERs per QALY gained for the comparison of IsaVRd versus DRd were isatuximab RDIs (during the continuous and induction phases) and subsequent treatment costs (following treatment with IsaVRd and following treatment with DRd). Patient weight also had a big effect on company model results.

Table 30 The five variables that had the biggest impact on ICERs per QALY gained (IsaVRd versus DRd) (list prices)

Rank	Parameter name	Difference between upper and lower bound ICERs per QALY gained
1	RDI of isatuximab IV during the continuous phase of treatment (0.68 to 1.00)	[redacted]
2	RDI induction isatuximab IV (0.68 to 1.00)	[redacted]
3	Subsequent treatment acquisition cost DRd (£46,511to £68,900)	[redacted]
4	Weight (72.14kg to 75.02kg)	[redacted]
5	Subsequent treatment acquisition cost IsaVRd (£36,139 to £53,535)	[redacted]

DRd=daratumumab+lenalidomide+dexamethasone; ICER=incremental cost effectiveness ratios; IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; IV=intravenous; QALY=quality adjusted life year; RDI=relative dose intensity
Source: company model EMA

5.2 Scenario analyses

The company ran 42 scenario analyses to explore the impact on cost effectiveness results of alternative model assumptions. Using list prices, only the following three company scenario analyses, all relating to different approaches to model TTD for patients treated with DRd, showed that treatment with IsaVRd did not dominate treatment with DRd:

- TTD: HR derived using mDOT/mPFS for DRd
- DRd TTD=PFS
- Naïve TTD curve for DRd

5.3 Validation

The validity and technical accuracy of the model was checked by an independent health economist using an extensive checklist.

Clinical experts were consulted to ensure that inputs were plausible/representative. An initial meeting with a UK clinical expert was followed by two advisory boards; these advisory boards were attended by seven and eleven clinical experts, respectively. Subsequently interviews were conducted with four UK clinical experts to inform the company IsaVRd and VRd OS and PFS extrapolations.

The company also compared modelled median OS and PFS results with known published results and Flatiron data.[22]

6 EAG CRITIQUE OF COMPANY ECONOMIC MODEL

The company submitted an economic model, developed in Microsoft® Excel, to generate cost effectiveness results for the comparison of IsaVRd versus DRd, VMP, Rd, and VCd for patients with NDMM who are not eligible for ASCT.

In response to the clarification letter, the company submitted a new model (referred to as the clarification model) and cost effectiveness results: Scenario A (60 months of IMROZ trial data); Scenario B (final OS DRd MAIA trial data).

The EAG critique focuses on the comparison of IsaVRd versus DRd as clinical advice to the company and the EAG is that DRd is the most relevant for patients with NDMM who are not eligible for ASCT. In line with the company's approach, EAG cost effectiveness results for the comparison of IsaVRd versus other comparators are available in Appendix 1 (Section 8.1).

6.1 Overview of modelling issues identified by the EAG

The EAG considers that the company clarification model is overly complicated due to the approach used to model OS and PFS for comparator treatments. Further, inefficient probabilistic sensitivity analysis (PSA) coding means that each PSA run (1000 iterations) takes up to 9 hours to complete. However, the EAG is satisfied that the company model algorithms are accurate, and, except for administration costs, parameter values used in the company model are reasonable.

A summary of the EAG's critique is presented in Table 31.

Table 31 Summary of the EAG critique of the company's cost effectiveness model

Aspect considered	EAG comment	Section of EAG report
Company model version	In response to clarification questions B1 to B4, the company provided cost effectiveness results for Scenario A (60 months of IMROZ trial data). The EAG considers that whilst Scenario A results were not generated in quite the way anticipated by the EAG, these results are still more informative than company base case results (presented in the CS). Therefore, EAG corrections have all be applied to Scenario A results; these results were generated using list prices for all drugs.	6
Model structure	• The company model structure and time horizon are appropriate	NA
Population and comparators	• The population modelled matches the final scope[2] issued by NICE • The most relevant comparator is DRd	NA

Aspect considered	EAG comment	Section of EAG report
Overall survival	• OS modelling for comparator treatments was overly complicated and use of time varying hazard ratios was unnecessary • OS for patients treated with IsaVRd is likely to be optimistic • There is insufficient clinical effectiveness evidence to support the modelling of an OS gain for patients treated with IsaVRd versus DRd **EAG revision**: Scenario A + setting OS for DRd to be equal to OS for IsaVRd **EAG revision**: Scenario A + use Gompertz distribution to model IsaVRd OS	6.3
Progression-free survival	• The company approach to modelling PFS for comparator treatments was overly complicated and the use of time varying hazard ratios was unnecessary • PFS for IsaVRd is likely to be optimistic **EAG revision**: Scenario A + use Gompertz distribution to model PFS for patients treated with IsaVRd	6.3
Time to treatment discontinuation	• The company approach to modelling of TTD for patients treated with IsaVRd and comparator treatments appears appropriate; however, some patients initially treated with IsaVRd spend an unusually long time in the PFS health state off active treatment **EAG revision:** Scenario A + DRd TTD set equal to IsaVRd TTD	6.4
Modelled subsequent treatments	• The long length of time that patients treated with IsaVRd and are off treatment but remain in the progression-free health state may not reflect NHS clinical practice • The subsequent treatments received do not reflect the introduction of SVd on the NHS in May 2024. **EAG scenario**: Scenario A + set subsequent treatments cost for patient treated to IsaDRd set the same as subsequent treatment costs for patients treated with DRd	6.4 and 6.6
Utility values	• Utility values in the post-progression health state are too pessimistic and there is insufficient justification for not using IMROZ trial progressed disease utility values **EAG revision**: Scenario A + use IMROZ trial progressed disease utility value	6.5
Drug costs	• The company has used assumed the values of confidential discounts for comparator treatments; all EAG cost effectiveness results have been generated using listed prices for all drugs • The EAG has no concerns about the ways that RDI and drug wastage were implemented in the model • The company used out of date drug administration costs **EAG revision**: Scenario A + up to date drug administration costs	6.7
Healthcare resource use	• The company has correctly applied costs and resource use for both treatment arms	NA
Adverse events	• The EAG is satisfied with the way AEs have been incorporated into the model, noting their removal makes minimal difference to the ICERs per QALY gained	NA

Aspect considered	EAG comment	Section of EAG report
Company severity modifier	• The company did not apply a severity modifier; the EAG agrees that this approach was appropriate	6.8
PSA	• The company PSA included variation of unit costs, which is inappropriate. EAG PSA runs have not varied unit costs	NA

AE=adverse event; EAG=External Assessment Group; ICER=incremental cost effectiveness analysis; NA=not applicable; NICE=National Institute for Health and Care Excellence; OS=overall survival; PFS=progression-free survival; PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year; RDI=relative dose intensity; TTD=time to treatment discontinuation

6.2 Company approach to modelling OS and PFS

The company fitted parametric distributions to IMROZ trial ITT population OS and PFS K-M data; the approach taken by the company was in line with NICE TSD 14 guidance.[37] The company considered that the most appropriate distributions to use to generate long-term survival estimates were the Gompertz distribution (OS) and the Gamma distribution (PFS).

The company jointly fitted distributions to MAIC adjusted IMROZ trial (IsaVRd) and comparator (DRd, VMP and Rd) trial OS and PFS K-M data. The company also jointly fitted distributions to IMROZ trial ITT (IsaVRd) and IPW adjusted VCd OS and PFS data. The company then estimated time-varying HRs by comparing intervention and comparator survival estimates at different time points. These HRs were applied to IMROZ trial ITT population OS (Gompertz) and PFS (Gamma) distributions to generate survival estimates for patients treated with DRd, VMP, Rd and VCd. The EAG considers that this approach was overly complicated and the fitted distributions used to estimate time-varying HRs could have been used directly in the company model.

As survival estimates based on IMROZ trial MAIC adjusted OS (and PFS) data are, at all time points, lower than survival estimates based on IMROZ trial ITT data, generating survival estimates based on IMROZ trial IsaVRd ITT OS (and PFS) K-M data generates optimistic OS estimates for IsaVRd. Further, IsaVRd OS estimates may be overly optimistic as distributions were fitted to all available data; the EAG considers that the company should only have fitted distributions to the first 60 months of data as, after 60 months, the only events remaining were censoring events.

To address both the over-complexity and over-optimistic nature of the company IsaVRd OS and PFS estimates, the EAG asked the company (clarification questions B1 to B4) to fit separate distributions to the first 60 months of MAIC adjusted IMROZ trial IsaVRd data and to comparator trial data and use these distributions in the company model. However, the company appears to have misinterpreted this request and has fitted joint distributions to 60

months of MAIC adjusted IMROZ trial IsaVRd and comparator trial PFS and OS data and then used these distributions to calculate time-varying HRs ratios for IsaVRd versus comparators. These HRs were then applied to distributions fitted to 60-month IMROZ trial ITT IsaVRd OS and PFS data. In summary, the only alteration to the original methods used by the company to generate company base case cost effectiveness results was the use of 60 months (rather than 5.67 years) of IMROZ trial data.

Company and clinician landmark OS and PFS IsaVRd survival estimates are shown in Table 32 and Table 33, respectively. The survival estimates that were generated using distributions fitted to 60 months of IMROZ trial IsaVRd OS and PFS K-M data were more in line with clinician landmark survival estimates than company estimates generated by fitting distributions to 5.67 years of IMROZ trial data. Therefore, cost effectiveness results generated based on 60 months of IMROZ trial data should be used to inform decision making.

Table 32 Overall survival: proportions of patients alive at key time points

Distribution	**Generated using IMROZ trial data**					
	5.67 years	**60 months**	**5.67 years**	**60 months**	**5.67 years**	**60 months**
	10 years		**15 years**		**20 years**	
Exponential	53.53%	55.17%	36.72%	35.82%	18.38%	17.93%
Gamma	53.55%	52.07%	36.84%	35.38%	18.39%	17.71%
Generalised gamma	51.70%	48.33%	34.50%	29.26%	17.30%	14.56%
Gompertz	52.36%	47.56%	35.40%	27.71%	17.74%	13.48%
Log-logistic	56.30%	55.17%	38.97%	37.95%	19.48%	19.00%
Log-normal	59.22%	58.61%	41.01%	40.31%	20.49%	20.18%
Weibull	53.42%	51.72%	36.62%	35.02%	18.33%	17.53%
Clinician estimates %, (95% CI)	45% (35% to 55%) Max: 60%		24% (15% to 33%) Max: 35%		11% (5% to 17%) Max: 20%	

CI=confidence interval; ITT=intention to treat
Source: company clarification response, Table 5

Table 33 Progression-free survival: proportions of patients progression-free at key time points

Distribution	Generated using IMROZ trial data					
	5.67 years	60 months	5.67 years	60 months	5.67 years	60 months
	10 years		15 years		20 years	
Exponential	40.60%	40.25%	25.67%	24.37%	17.61%	12.12%
Gamma	40.20%	39.60%	25.19%	23.92%	12.61%	11.90%
Generalised gamma	40.79%	39.11%	26.09%	23.47%	13.06%	11.68%
Gompertz	40.62%	38.59%	25.69%	22.58%	12.86%	11.23%
Log-logistic	44.71%	42.36%	30.12%	25.65%	15.08%	12.76%
Log-normal	46.39%	42.15%	31.25%	26.13%	15.65%	13.00%
Weibull	40.15%	39.44%	25.10%	23.78%	12.57%	11.83%
Clinician estimates %, (95% CI)	28% (23% to 33%) Max: 40%		11% (2% to 16%) Max: 20%		2% (0% to 6%) Max: 10%	

CI=confidence interval; ITT=intention to treat
Source: company clarification response, Table 11

Based on 60 months of IMROZ trial data, the company chose the generalised gamma distribution to generate OS estimates. The EAG highlights that the Gompertz distribution is a better fit based on Akaike information criterion and Bayesian Information Criterion statistics (company clarification response, Table 4) and generates OS estimates that are closer to clinician landmark estimates. The EAG therefore considers that the Gompertz distribution should be used to generate OS estimates for patients treated with IsaVRd.

Based on 60 months of IMROZ trial data, the company chose the Weibull distribution to generate IsaVRd PFS estimates. The EAG considers that the Gompertz distribution is a better choice as it is comparatively ranked (company clarification response, Table 10) and generates estimates that are more closely aligned to clinical expert opinion than the Weibull distribution.

To remove the complexity associated with generating survival estimates using time-varying HRs, the EAG considered using constant HR MAIC results; however, these were not provided (or explicitly requested) as part of the company clarification response. The EAG considers that as the company's original cost effectiveness results (presented in the CS) were insensitive to whether constant or time-varying HRs were used, cost effectiveness results generated using the company clarification model are also likely to be insensitive to whether constant or time-varying HRs are used.

6.3 Overall survival: IsaVRd and DRd

The EAG considers that the available clinical effectiveness evidence does not strongly support the assumption that patients treated with IsaVRd live longer than patients treated with DRd. All OS HRs presented by the company (CS and clarification response) for the comparison of IsaVRd versus DRd are close to 1 and are not statistically significantly different from 1. MAIC adjusted IsaVRd OS data (5.67 years) and MAIA trial DRd OS data are shown in Figure 3.

Figure 3 OS K-M plots: IsaVRd (IMROZ trial unadjusted and MAIC adjusted) versus DRd (MAIA trial) data

K-M=Kaplan-Meier; MAIC=matching-adjusted indirect comparison; OS=overall survival
Source: CS, Figure 23

Data presented in Figure 3 show that between 0 and 12 months and between 36 and 60 months survival rates are almost identical for patients treated with IsaVRd and DRd. However, as shown in Table 34, the company has modelled a survival benefit for patients treated with IsaVRd over the whole model time horizon with [redacted]% more patients alive at 12 months, [redacted]% more patients alive at 3 years and [redacted]% more patients alive at 5 years when treated with IsaVRd compared to DRd. The EAG highlights that the MAIC adjusted analysis provides evidence that there would be no survival difference between treatments at these time-points. Whilst the survival differences appear small, the company life year gain estimates account for approximately [redacted]% of the total QALY gain for the comparison of IsaVRd versus DRd. The EAG

therefore considers that modelling a survival benefit over the first 12 months and beyond 36 months is not supported by the available evidence.

Table 34 Company modelled IsaVRd and DRd overall survival at key time points

	IsaVRd	DRd
1 year	[redacted]	[redacted]
2 years	[redacted]	[redacted]
3years	[redacted]	[redacted]
5 years	[redacted]	[redacted]
10 years	[redacted]	[redacted]

DRd=daratumumab+lenalidomide+dexamethasone; IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone
Source: company model

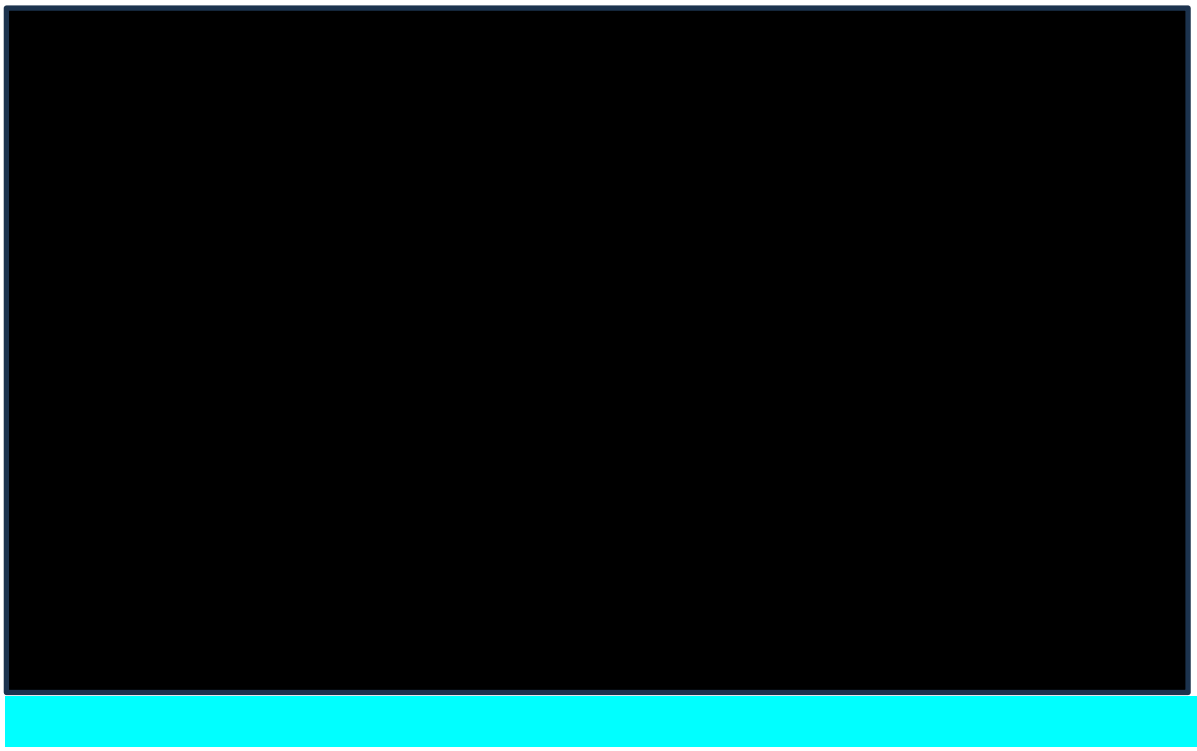
The EAG highlights that mortality rates appear to be higher for patients treated with DRd between months 12 and 24, and higher for patients treated with IsaVRd between months 24 and 36. The EAG asked the company to provide a clinical rationale to explain the apparent fluctuation in mortality rates over time that supports these differences being more than a statistical artefact (clarification question A4).

The company responded that differences may have been due to COVID-19 deaths (n=12). The EAG considers that as the number of COVID-19 deaths was low, it seems unlikely that this fully explains the fluctuations. Nor does this rationale explain why mortality hazards from month 36 onwards are essentially identical for patients treated with IsaVRd and patients treated with DRd.

In summary, the EAG considers that no OS gain should be modelled for IsaVRd over DRd and has set OS for DRd to be equal to IsaVRd.

6.4 Difference between PFS and TTD for patients treated with IsaVRd

The company has modelled PFS to be substantially longer for patients treated with IsaVRd (median=[redacted]) compared to DRd (median=[redacted]), despite modelled TTD being slightly lower for patients treated with IsaVRd (median=[redacted]) compared to DRd (median=[redacted]). This means that the modelled PFS curve for IsaVRd is substantially above the modelled TTD curve whereas the modelled DRd PFS curve is only slightly above the modelled DRd TTD curve (Figure 4).



DRd=daratumumab+lenalidomide+dexamethasone; IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; PFS=progression-free survival; TTD=time to treatment discontinuation
Source: company clarification model

Figure 4 Company modelled IsaVRd and DRd PFS and TTD

The EAG asked the company (clarification question A3) to provide a clinical rationale to explain why TTD appears to be slightly longer for patients treated with DRd compared to patients treated with IsaVRd (CS, Figure 24) whereas PFS appears to be substantially longer for patients treated with IsaVRd than for patients treated with DRd (CS, Figure 23). The company responded that the quadruplet therapy delivered during the treatment induction phase explains the longer PFS for patients treated with IsaVRd than for patients treated with DRd (which is a triplet therapy). The company considered that as, after the induction phase, i.e., during the treatment maintenance phase, IsaVRd becomes a triplet therapy (IsaRd) and as both treatments are then triplet therapies tolerability will be similar. The EAG considers that this only explains why PFS for patients treated with IsaVRd might be longer than PFS for patients treated with DRd but does not explain why TTD might be the same for the two treatments.

Both IsaVRd and DRd are treatment to progression regimens. Therefore, if patients stop treatment before progression, it can be assumed that some part of the regimen has become intolerable to patients. However, in terms of Grade ≥3 AEs (CS, Table 59), the DRd AE profile appears less favourable than the IsaVRd AE profile. Therefore, the EAG expects that TTD for patients treated with IsaVRd would be longer than TTD for patients treated with DRd.

However, given the lack of statistical evidence that TTD is different for patients treated with IsaVRd and DRd, the EAG has also set TTD to be equal.

In the company clarification model, for patients treated with IsaVRd, at 5 years, [redacted]% of patients are in the PFS health state and [redacted]% are still on treatment, i.e., [redacted]% of the cohort are progression free but no longer receiving IsaVRd. For patients treated with DRd, at 5 years, [redacted]% of patients are in the PFS health state and [redacted]% are still on treatment, i.e., [redacted]% of the cohort are progression free but no longer receiving DRd.

If, after 5 years, all model progression events only relate to patients in the progression-free health state who are off treatment:

- for patients treated with IsaVRd, the median time to progression would be [redacted] and the last progression event will occur [redacted] after stopping treatment.
- for patients treated with DRd, the median time to progression would be [redacted] and last progression event would be at [redacted] after stopping treatment.

Clinical advice to the EAG is that whilst extended PFS for patients with a deep response despite coming off treatment is not implausible, the proportion of patients who experience extended PFS when off treatment and the length of the extended PFS is not known. Therefore, the EAG has not made any revisions to the model but highlights that, if the difference between PFS and TTD modelled for patients treated with IsaVRd is not reflected in NHS practice or, if patients who stop treatment with IsaVRd receive subsequent treatments before progression, then the total cost associated with treatment with IsaVRd estimated by the company, and therefore the ICERs per QALY gained for IsaVRd versus comparators, will be underestimates.

The company has used IMROZ and MAIA[28] trial ITT data to estimate the proportion of patients who receive subsequent treatments. As there are differences in key patient characteristics between these three trials, a naïve analysis without adjusting for these differences is likely to be confounded.

The EAG has the following concerns relating to the company approach to modelling PFS and TTD:

- the length of time the company has modelled patients treated with IsaVRd being progression free and not receiving active treatment
- how rates of subsequent treatments for patients treated with IsaVRd and DRd have been calculated a
- TTD for patients treated with IsaVRd and DRd are modelled to be almost identical.

The EAG has therefore set total subsequent treatment costs for patients treated with IsaVRd to be the same as total subsequent treatment costs for patients treated with DRd (EAG

Scenario 1). The EAG considers that the true ICERs per QALY gained for IsaVRd versus the comparators will lie somewhere between this scenario and the company base case.

6.5 Utility values

The EAG considers that the utility values used by the company to represent HRQoL in the post-progression health state are too low.

The company has used IMROZ trial data to estimate utility for patients in the PFS health state and the utility value used in the TA587[31] model (lenalidomide plus dexamethasone for previously untreated MM) to estimate utility for patients in the progressed-disease health state. IMROZ trial data were not used to represent utility for patients in the post-progression health state as the company considered that the IMROZ trial post-progression health state utility value was overly optimistic and that this utility value was not robust as it was derived from a small number of patients.

The EAG disagrees with both these assertions. First, IMROZ trial post-progression HRQoL data were available from 97 patients with progressed disease (272 records, 79% of these records were completed within 6 months of the progression event); the EAG does not consider that this is a small sample. Second, the IMROZ trial post-progression utility value is similar to the utility values used in the TA974[55] model (selinexor with bortezomib and dexamethasone [SVd] for treating relapsed refractory multiple myeloma). The TA974[55] values were sourced from the BOSTON[56] trial (patients who had received one or more previous treatments). The EAG therefore considers that the TA974[55] values may be generalisable to patients treated in the second-line or subsequent-line settings. The TA974[55] model PFS values were 0.7 (SVd) and 0.694 (Vd) and the TA974[55] progressed-disease value, was 0.660.

The company used the TA587[31] model progressed-disease utility value to estimate utility for patients in the post-progression health state. However, the TA587[31] model PFS utility values were derived from FIRST[29] trial data (0.504 after 16 weeks and only rising to 0.632 for patients remaining progression-free at 32 weeks) and were very low compared to the IMROZ trial PFS utility values. The EAG therefore considers that the FIRST[29] trial post-progression disease utility value (0.557) should not be used to represent utility for IMROZ trial IsaVRd patients in the post-progression health state.

The EAG considers that the approach taken by the company to select PFS utility values was appropriate. The EAG has, however, used the IMROZ trial pooled Independent Central Review PPS value ([redacted]) to represent utility for patients treated with IsaVRd and DRd. As this utility value is higher than the PFS utility values used for other comparator treatments, the

EAG has applied the utility decrement experienced by patients treated IsaVRd and DRd on moving to the post-progression health state ([redacted]) to the PFS value for the other comparator treatments. Company and EAG utility values are shown in Table 35.

Table 35 Company and EAG utility values*

	IsaVRd	DRd	VMP	Rd	VCd	Source
Company						
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IMROZ trial data
PPS	0.557	0.557	0.557	0.557	0.557	TA587[31]
EAG						
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IMROZ trial data
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IMROZ trial data

* Assumed that IsaVRd utility values can be used to represent HRQoL for patients treated with DRd and that VRd utility values can be used to represent HRQoL for patients treated with VMP, Rd and VCd
DRd=daratumumab+lenalidomide+dexamethasone; IsaVRd=isatuximab+bortezomib+lenalidomide+dexamethasone; PFS=progression-free survival; PPS=post-progression survival; Rd=lenalidomide+dexamethasone; VCd=bortezomib+cyclophosphamide+dexamethasone; VMP=bortezomib+melphalan+dexamethasone

Source: CS, Table 64 and EAG calculations

6.6 SVd as a subsequent treatment

The company has not included SVd as a second- or third-line treatment despite it having been recommended by NICE in May 2024 (TA974[55]). The EAG considers that SVd would be an effective second- or third-line treatment for patients that are focus of this appraisal. The impact of failing to include the costs and benefits of SVd on cost effectiveness results is not known.

6.7 Drug administration costs

The company has used NHS Reference Costs 2022/23[48] to estimate drug administration costs; these were adjusted for inflation. More up to date costs are available from NHS Cost Collection 2023/24.[57] The CS, company model and EAG costs per administration are shown in Table 36.

Table 36 Administration types and associated costs: company and EAG values

	Company			EAG	
	Cost per administration		Source: NHS Reference Costs 2022/23[48]	Cost per administration	Source: NHS Cost Collection 2023/24[57]
	CS Table 66	Company model			
IV - First dose	£486.10	£502.15	Total HRG: SB13Z – Deliver more complex parenteral chemotherapy at first attendance	£509	Total HRG: SB13Z – Deliver more complex parenteral chemotherapy at first attendance
IV - Prolonged first dose	£544.86	£562.84	Total HRG: SB14Z - Deliver complex chemotherapy, including prolonged	£598	Total HRG: SB14Z – Deliver complex chemotherapy, including

	Company			EAG	
	Cost per administration		Source: NHS Reference Costs 2022/23[48]	Cost per administration	Source: NHS Cost Collection 2023/24[57]
	CS Table 66	Company model			
			infusional treatment, at first attendance		prolonged infusional treatment, at first attendance
IV - Subsequent dose	£393.16	£406.14	Total HRG: SB15Z – Deliver subsequent elements of a chemotherapy cycle	£430	Total HRG: SB15Z – Deliver subsequent elements of a chemotherapy cycle
SC - First and subsequent doses	£411.99	£425.59	Total HRG: SB12Z – Deliver simple parenteral chemotherapy at first attendance	£394	Total HRG: SB12Z – Deliver simple parenteral chemotherapy at first attendance
Oral - First dose	£322.00	£332.62	Total HRG: SB11Z – Deliver exclusively oral chemotherapy	£283.00	Total HRG: SB11Z – Deliver exclusively oral chemotherapy
Oral - Subsequent dose	£0.00	£0.00	Assumption	£0.00	Assumption

CS=company submission; EAG=External Assessment Group; HRG=healthcare resource group; IV=intravenous; NHS=National Health Service
Source: CS, Table 66, company model and NHS Cost Collection 2023/24[57]

6.8 Severity modifier

The EAG agrees with the company that it is not appropriate to apply a severity modifier.

6.9 Impact of EAG revisions on company base case cost effectiveness results

In response to clarification questions B1 to B4, the company provided cost effectiveness results for Scenario A (60 months of IMROZ trial data). The EAG considers that whilst Scenario A results were not generated in quite the way anticipated by the EAG, these results are still more informative than company base case results (presented in the CS). Therefore, EAG corrections have all be applied to Scenario A results; these results were generated using list prices for all drugs.

The company has also generated results using final OS DRd MAIA trial data (Scenario B). The EAG considers that as IMROZ trial becomes more mature a comparison of IsaVRd versus DRd using final MAIA trial data will be informative.

The EAG has made the following revisions to the company clarification model (Scenario A):

- Set OS for DRd to be equal to OS for IsaVRd (R1)

- Used the Gompertz distribution to model IsaVRd OS (R2)
- Used the Gompertz distribution to model IsaVRd PFS (R3)
- For the progressed disease state, used utility values derived from the IMROZ trial (R4)
- Made TTD for DRd the same as for IsaVRd (R5)
- Used up to date administration costs (R6)
- Run a scenario in which total IsaVRd subsequent treatment costs are equal to DRd subsequent treatment costs (S1).

For PSA, the EAG has not varied any costs in the model.

Details of how the EAG revised the company model are presented in Appendix 2, Section 8.2 of this EAG report. Deterministic cost effectiveness results for the comparison of IsaVRd versus DRd are provided in Table 38 and probabilistic cost effectiveness results for company Scenario A and the EAG preferred base case are presented in Table 39. Results for the comparison of IsaVRd versus VMP, Rd and VCd are presented in Appendix 1 (Section 8.1). All results have been generated using list prices for all drugs.

All results tables have been replicated in the confidential appendix and the analyses include all confidential commercial arrangements as described in Table 37.

Table 37 Pricing sources used in the confidential appendix

Treatment	Price source/type of commercial arrangement
Bortezomib	Regional MPSC prices
Carfilzomib	PAS
Daratumumab	PAS and CAA
Isatuximab	PAS
Ixazomib	PAS
Panobinostat	PAS
Pomalidomide	PAS

CAA=Commercial Access Agreement; MPSC=Medicines Procurement and Supply Chain; PAS=Patient Access Scheme

Table 38 Deterministic cost effectiveness results for IsaVRd versus DRd, list prices for all drugs

EAG revisions	IsaVRd		DRd		Incremental		ICER per QALY gained	NMB*	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs			
A. Company CS base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**IsaVRd dominates**	[redacted]	
Company clarification response: Scenario A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**IsaVRd dominates**	[redacted]	[redacted]
R1) Scenario A + DRd OS set equal to IsaVRd OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]
R2) Scenario A + Gompertz to model IsaVRd OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]
R3) Scenario A + Gompertz to model IsaVRd PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]
R4) Scenario A + PD utility value from IMROZ trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]
R5) Scenario A + DRd TTD set equal to IsaVRd TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]
R6) Scenario A + updated drug administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]
B. EAG preferred base case (Scenario A + R1-R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**IsaVRd dominates**	[redacted]	[redacted]
EAG scenarios									
S1) Scenario A + IsaVRd total subsequent treatment costs set equal to DRd total subsequent treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]
S2) Scenario A + B+S1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IsaVRd dominates	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY

CS=company submission; DRd=daratumumab plus lenalidomide plus dexamethasone; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IsaVRd=isatuximab plus bortezomib plus lenalidomide plus dexamethasone; NMB=net monetary benefit; OS=overall survival; PD=progressed disease; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation

Table 39 Probabilistic cost effectiveness results for IsaVRd versus DRd, list prices for all drugs

EAG revisions	IsaVRd		DRd		Incremental		ICER per QALY gained	NMB*	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs			
A. Company CS base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**IsaVRd dominates**	[redacted]	
B. EAG preferred base case (Scenario A + R1-R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**IsaVRd dominates**	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY

CS=company submission; DRd=daratumumab plus lenalidomide plus dexamethasone; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IsaVRd=isatuximab plus bortezomib plus lenalidomide plus dexamethasone; NMB=net monetary benefit; QALY=quality adjusted life year

6.10 Cost effectiveness conclusions

The company OS and PFS estimates for patients treated with IsaVRd and comparators were generated using methods that were overly complex and may have overestimated the OS and PFS gains for patients treated with IsaVRd. However, compared to treatment with DRd, the EAG considers that there is insufficient clinical effectiveness evidence to support an OS gain for patients treated with IsaVRd; however, there is sufficient clinical effectiveness evidence to support a PFS gain. In the company model, longer PFS for patients treated with IsaVRd leads to higher total QALYs as the PFS health state utility value is higher than the post-progression health state utility value. Longer PFS for patients treated with IsaVRd also leads to lower subsequent treatment costs as IsaVRd and DRd are treatment to progression regimens. The EAG considers that the utility gain in the PFS health state has been over-stated by the company. The EAG is also concerned that the avoidance of subsequent treatment costs may also have been over-stated by the company.

The company base case cost effectiveness results (presented in the CS) showed that the QALY gain for patients treated with IsaVRd versus DRd was not substantial; company clarification base case (Scenario A) QALY gains and EAG preferred base case QALY gains were even lower. Relative cost effectiveness is therefore very sensitive to IsaVRd and DRd (commercially confidential) drug costs.

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8 APPENDICES

8.1 Appendix 1: EAG cost effectiveness results: IsaVRd versus VMP, Rd and VCd

Table 40 Deterministic cost effectiveness results for IsaVRd versus VMP, list prices for all drugs

EAG revisions	IsaVRd		VMP		Incremental		ICER per QALY gained	NMB*	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs			
A. Company CS base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£98,035**	[redacted]	-
Company clarification response: Scenario A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£101,171**	[redacted]	[redacted]
R2) Scenario A + Gompertz to model IsaVRd OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£102,336	[redacted]	[redacted]
R3) Scenario A + Gompertz to model IsaVRd PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£101,534	[redacted]	[redacted]
R4) Scenario A + PD utility value from IMROZ trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£111,759	[redacted]	[redacted]
R6) Scenario A + updated administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£101,882	[redacted]	[redacted]
B. EAG preferred base case (Scenario A + R2-R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£114,008**	[redacted]	[redacted]
EAG scenarios									
S1) Scenario A + IsaVRd total subsequent treatment costs set equal to DRd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£105,209	[redacted]	[redacted]
S2) Scenario A + B + S1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£118,440	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY

CS=company submission; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IsaVRd=isatuximab plus bortezomib plus lenalidomide plus dexamethasone; NMB=net monetary benefit; OS=overall survival; PD=progressed disease; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation; VMP=bortezomib, melphalan and prednisone

Table 41 Probabilistic cost effectiveness results for IsaVRd versus VMP, list prices for all drugs

EAG revisions	IsaVRd		VMP		Incremental		ICER per QALY gained	NMB*	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs			
A. Company CS base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£108,920**	[redacted]	
B. EAG preferred base case (Scenario A + R2-R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£127,148**	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY

CS=company submission; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IsaVRd=isatuximab plus bortezomib plus lenalidomide plus dexamethasone; NMB=net monetary benefit; QALY=quality adjusted life year; VMP=bortezomib, melphalan and prednisone

Table 42 Deterministic cost effectiveness results for IsaVRd versus Rd, list prices for all drugs

EAG revisions	IsaVRd		Rd		Incremental		ICER per QALY gained	NMB*	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs			
A. Company CS base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£172,089**	[redacted]	-
Company clarification response: Scenario A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£176,449**	[redacted]	[redacted]
R2) Scenario A + Gompertz to model IsaVRd OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£176,925	[redacted]	[redacted]
R3) Scenario A + Gompertz to model IsaVRd PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£177,275	[redacted]	[redacted]
R4) Scenario A + PD utility value from IMROZ trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£200,056	[redacted]	[redacted]
R6) Scenario A + updated drug administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£178,400	[redacted]	[redacted]
B. EAG preferred base case (Scenario A + R2-R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£202,548**	[redacted]	[redacted]
EAG scenarios									
S1) Scenario A + IsaVRd total subsequent treatment costs set equal to DRd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£182,609	[redacted]	[redacted]
S2) Scenario A + B + S1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£209,410	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY

CS=company submission; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IsaVRd=isatuximab plus bortezomib plus lenalidomide plus dexamethasone; NMB=net monetary benefit; OS=overall survival; PD=progressed disease; PFS=progression-free survival; QALY=quality adjusted life year; Rd=lenalidomide plus dexamethasone; TTD=time to treatment discontinuation

Table 43 Probabilistic cost effectiveness results for IsaVRd versus Rd, list prices for all drugs

EAG revisions	IsaVRd		Rd		Incremental		ICER per QALY gained	NMB*	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs			
A. Company CS base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£188,467**	[redacted]	
B. EAG preferred base case (Scenario A + R2-R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£234,285**	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY

CS=company submission; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IsaVRd=isatuximab plus bortezomib plus lenalidomide plus dexamethasone; NMB=net monetary benefit; QALY=quality adjusted life year; Rd=lenalidomide plus dexamethasone

Table 44 Deterministic cost effectiveness results for IsaVRd versus VCd, list prices for all drugs

EAG revisions	IsaVRd		VCd		Incremental		ICER per QALY gained	NMB*	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs			
A. Company CS base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£113,326**	[redacted]	-
Company clarification response: Scenario A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£126,328**	[redacted]	[redacted]
R2) Scenario A + Gompertz to model IsaVRd OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£127,562	[redacted]	[redacted]
R3) Scenario A + Gompertz to model IsaVRd PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£126,800	[redacted]	[redacted]
R4) Scenario A + PD utility value from IMROZ trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£133,006	[redacted]	[redacted]
R6) Scenario A + updated administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£127,725	[redacted]	[redacted]
B. EAG preferred base case (Scenario A + R2-R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£136,000**	[redacted]	[redacted]
EAG scenarios									
S1) Scenario A + IsaVRd total subsequent treatment costs set equal to DRd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£130,769	[redacted]	[redacted]
S2) Scenario A + B + S1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£140,640	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY

CS=company submission; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IsaVRd=isatuximab plus bortezomib plus lenalidomide plus dexamethasone; NMB=net monetary benefit; OS=overall survival; PD=progressed disease; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation; VCd=bortezomib with cyclophosphamide and dexamethasone

Table 45 Probabilistic cost effectiveness results for IsaVRd versus VCd, list prices for all drugs

EAG revisions	IsaVRd		VCd		Incremental		ICER per QALY gained	NMB*	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs			
A. Company CS base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£125,259**	[redacted]	
B. EAG preferred base case (Scenario A + R2-R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£147,788**	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY

CS=company submission; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IsaVRd=isatuximab plus bortezomib plus lenalidomide plus dexamethasone; NMB=net monetary benefit; QALY=quality adjusted life year; VCd=bortezomib with cyclophosphamide and dexamethasone

8.2 Appendix 2: EAG revisions to the company model

This appendix contains details of the changes that the EAG made to the company clarification model.

EAG revisions	Implementation instructions
Set up EAG revision switches	**Insert Sheet 'EAG Amendments'** Set cell B3 = "R1 – OS for IsaVRd equal to DRd " Name cell C3 = "EAG_R1" Set cell B5 = "R2 – gompertz to model IsaVRd OS" Name cell C5 = "EAG_R2" Set cell B7 = "R3 – gompertz to model IsaVRd PFS" Name cell C7 = "EAG_R3" Set cell B8 = "R4 – PD utility values from IMROZ trial" Name cell C8 = "EAG_R4" Set cell B9 = "R5 – DRd TTD set equal to IsaVRd" Name cell C9 = "EAG_R5" Set cell B10 = "R6 –update administration costs" Name cell C10 = "EAG_R6" Set cell B11 = "S1 – IsaVRd subsequent treatment costs equal to DRd" Name cell C11 = "EAG_S1"
R1) OS DRd set equal to IsaVRd	**In Sheet 'EAG Amendments'** **Set cell C3 = 1** **In Sheet 'Trace DRd'** Set cell S22 =IF(EAG_R1=1,'Trace (IVRd)'!S22,INDEX(OS!$F$150:$T$150,$S$6)) Set cell S23 =if(EAG_R1=1,'Trace (IVRd)'!S23,INDEX(OS!F151:T151,$S$6)) Copy cell S23 Paste to S24:S1066
R2) Gompertz to model IsaVRd OS	**In Sheet 'EAG Amendments'** **Set cell C5 = 1** **In Sheet 'Controls'** In cell I262, clear validation rules Set cell I262= IF(EAG_R2=1,"Gompertz","Generalised gamma")
R3) Gompertz to model IsaVRd PFS	**In Sheet 'EAG Amendments'** **Set cell C7 = 1** **In Sheet 'Controls'** In cell I201, clear validation rules Set cell I201= IF(EAG_R3=1,"Gompertz","Weibull")

R4) PD utility values from IMROZ trial	**In Sheet 'EAG Amendments'** Set cell C8 = 1 **In Sheet 'Controls'** In cell I162, clear validation rules Set cell I162= IF(EAG_R4=1,"IMROZ (EQ-5D-3L)","Literature")
R5) DRd TTD set equal to IsaVRd	**In Sheet 'EAG Amendments'** Set cell C9 = 1 **In Sheet 'Controls'** Set cell F332 =IF(EAG_R5=1,1,CHOOSE(match_TTD_method_DRd,G332,I332,"NA","NA",K332))
R6) Update administration costs	**In Sheet 'EAG Amendments'** Set cell C10 = 1 **In Sheet "Drug costs'** Set cell J238 =IF(EAG_R6=1,509,INDEX(p_adm_array_costs,C238)) Set cell J239 =IF(EAG_R6=1,598,INDEX(p_adm_array_costs,C239)) Set cell J240 =IF(EAG_R6=1,430,INDEX(p_adm_array_costs,C240)) Set cell J243 =IF(EAG_R6=1,394,INDEX(p_adm_array_costs,C241)) Set cell J244 =IF(EAG_R6=1,283,INDEX(p_adm_array_costs,C242))
S1) IsaVRd subsequent treatment costs equal to DRd	**In Sheet 'EAG Amendments'** **Set cell B7 = 1** **In Sheet 'Trace IsaVRd'** Set cell DG18 =IF(EAG_S1=1,'Trace (DRd)'!CS18,SUMIF($N$22:$N$1066,"<="&misc_timeHorizon,DG$22:DG$1066)) Set cell DJ18 =IF(EAG_S1=1,'Trace (DRd)'!CV18,SUMIF($N$22:$N$1066,"<="&misc_timeHorizon,DJ$22:DJ$1066)) Set cell FG18=IF(EAG_S1=1,'Trace (DRd)'!ES18,SUMIF($N$22:$N$1066,"<="&misc_timeHorizon,FG$22:FG$1066)) Set cell FI18=IF(EAG_S1=1,'Trace (DRd)'!EU18,SUMIF($N$22:$N$1066,"<="&misc_timeHorizon,FI$22:FI$1066))

Turn off costs for PSA	**In Sheet 'Parameters'** Set cells (where values) G205:G211, G349:G432, G824: = "No"

Single Technology Appraisal

Isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 03/03/2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as ‘[redacted]’ in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
P13 "Seek clinical advice on OS for patients treated with IsaVRd and patients treated with DVd" DVd is not the same regimen as DRd. "V" is used for Velcade (bortezomib) whereas R is used for Revlimid (lenalidomide)	"Seek clinical advice on OS for patients treated with IsaVRd and patients treated with DRd"	Typographical error	This is a typographical error. The text in the EAG report has been amended to 'DRd' as advised.

Issue 2

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG Response</th></tr>
<tr><td>P16, Tables B, C, D and E
Company base case following clarification</td><td>Table B Probabilistic pairwise results (IsaVRd versus DRd), list prices for all drugs
<table>
<tr><th rowspan="2">EAG revisions</th><th colspan="2">Incremental</th><th rowspan="2">ICER £/QALY</th><th rowspan="2">NMB (WTP=£30,000)</th></tr>
<tr><th>Costs</th><th>QALYs</th></tr>
<tr><td>A1. Company CS base case</td><td>[redacted]</td><td>[redacted]</td><td>IsaVRd dominates</td><td>[redacted]</td></tr>
<tr><td>A2. Company base case following clarification questions</td><td>[redacted]</td><td>[redacted]</td><td>IsaVRd dominates</td><td>[redacted]</td></tr>
</table></td><td>The company base-case has been updated in the responses to the</td><td>As the company clarification response did not specify a new base</td></tr>
</table>

questions is missing from the tables		clarification questions	case, no changes have been made to the EAG report.

B1. EAG preferred base case	[redacted]	[redacted]	**IsaVRd dominates**	[redacted]

Table C Probabilistic pairwise results (IsaVRd versus VMP), list prices for all drugs

EAG revisions	Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Costs	QALYs		
A1. Company CS base case	[redacted]	[redacted]	**£108,920**	[redacted]
A2. Company base case following clarification questions	[redacted]	[redacted]	**£111,638**	[redacted]
B1. EAG preferred base case	[redacted]	[redacted]	**£127,148**	[redacted]

Table D Probabilistic pairwise results (IsaVRd versus Rd), list prices for all drugs

EAG revisions	Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Costs	QALYs		
A1. Company CS base case	[redacted]	[redacted]	**£188,467**	[redacted]
A2. Company base case following clarification questions	[redacted]	[redacted]	**£210,387**	[redacted]
B1. EAG preferred base case	[redacted]	[redacted]	**£234,285**	[redacted]

Table E Probabilistic pairwise results (IsaVRd versus VCd), list prices for all drugs

EAG revisions	Incremental		ICER £/QALY	NMB (WTP=£30,000)
	Costs	QALYs		
A1. Company CS base case	[redacted]	[redacted]	**£125,259**	[redacted]
A2. Company base case following clarification questions	[redacted]	[redacted]	**£137,357**	[redacted]
B1. EAG preferred base case	[redacted]	[redacted]	**£147,788**	[redacted]

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
P33 "The company was unable to interpret the HR for patients with chromosomal abnormality t(14;16) due to small patient numbers (>10)." The HR was not interpreted because the number of patients was smaller than 10, not greater	"The company was unable to interpret the HR for patients with chromosomal abnormality t(14;16) due to small patient numbers (<10)."	Typographical error	This was a typographical error. The EAG report has been amended as advised.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
P40 "The EAG highlights that time varying MAIC HRs were used in the company's base case economic analyses; however, these	"The EAG highlights that time-varying MAIC HRs were used in the company's base case economic analyses. These results were presented in the company's submission (CS) in Tables 51 and 55, and additional details, including	Time-varying HRs versus all comparators and for all distributions were presented as part of company's clinical effectiveness evidence base	The text has been amended as advised.

results were not presented as part of the company's clinical effectiveness evidence base." Time-varying MAIC HRs were presented in the CS, Tables 51 and 55. Landmark HRs and figures illustrating time-varying HRs over time for all distributions can be found in Appendix, Tables 98-105 and Figures 80-87.	landmark HRs and figures illustrating time-varying HRs over time for all distributions, can be found in the Appendix (Tables 98-105 and Figures 80-87)."		

Issue 5

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG Response</th></tr>
<tr>
<td>P49, Table 18

Curve selection has been updated for OS following the</td>
<td>
<table>
<tr><th>Endpoint</th><th>Curve selection</th><th>Company brief rationale</th></tr>
<tr><td>PFS</td><td>Weibull</td><td>The gamma, Gompertz and Weibull distributions provided the most plausible estimates; the Gamma distribution was chosen due to having the best statistical fit</td></tr>
<tr><td>OS</td><td>Submission: Gompertz

Clarification</td><td>Generalised gamma and Gompertz distributions provided the most plausible estimates; however, the statistical fit of the</td></tr>
</table>
</td>
<td>Base-case has been updated following the clarification questions</td>
<td>As the company clarification response did not specify a new base case, no</td>
</tr>
</table>

clarification questions.		questions: Generalised Gamma	Gompertz distribution was better than that of the generalised gamma distribution Following the clarification questions, the Generalised gamma distribution was selected to align the choice of distribution with the committee's preferred distribution to extrapolate DRd in TA917		changes have been made to the EAG report.
	TTD	Exponential	Best statistical fit		

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
P49 "For the period from the end of the IMROZ trial follow-up to the end of the model time horizon, the HRs were fixed" Sentence suggest that HR was fixed at the end of the follow-up for OS and PFS.	"For OS only and for the period from the end of the IMROZ trial follow-up to the end of the model time horizon, the HR was fixed."	The HR was fixed for OS only, in line with TA917.	The EAG report has been amended as advised.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
P59 "Further, inefficient probabilistic sensitivity analysis (PSA) coding means that each PSA run (1000 iterations) takes up to 9 hours to complete." PSA and CEAC completed in 2h35min in the clarification model for 700 iterations.	Suggest deleting the sentence	Incorrect time taken to run the PSA and the CEAC	This is not a factual inaccuracy. No change has been made to the EAG report.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
P64 Survival rates seem to have been extracted incorrectly. "However, as shown in Table 34, the company has modelled a survival benefit	"However, as shown in Table 34, the company has modelled a survival benefit for patients treated with IsaVRd over the whole model time horizon with [redacted]% more patients alive at 12 months, [redacted]% more patients alive at 3 years and [redacted]% more patients alive at	Incorrect survival rates	The EAG report has been amended as advised.

for patients treated with IsaVRd over the whole model time horizon with [redacted]% more patients alive at 12 months, [redacted]% more patients alive at 3 years and [redacted]% more patients alive at 5 years when treated with IsaVRd compared to DRd.”	5 years when treated with IsaVRd compared to DRd.”		

Issue 9

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG Response**
P65, Table 34 Survival rates seem to have been extracted incorrectly.	See table below	Incorrect survival rates	The EAG report has been amended as advised.

	IsaVRd	**DRd**
1 year	[redacted]	[redacted]
2 years	[redacted]	[redacted]
3years	[redacted]	[redacted]
5 years	[redacted]	[redacted]
10 years	[redacted]	[redacted]

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
P67 "Further, as the IMROZ trial follow up is shorter than the MAIA[28] trial follow-up, there is less time for IMROZ trial patients who have progressed to start subsequent treatment." Data extracted from IMROZ and MAIA to estimate a proportion of patients with a subsequent treatment are based on the same follow-up (median of 59.7 months and 56.2 months, respectively). Additionally, the rate of patients with a subsequent treatment has been derived as a rate of patients among those with a PFS event (not among all initial patients). This is to	Suggest deleting the sentence	Incorrect as data extracted to estimate the proportion of patients with a subsequent treatment are based on a very similar follow-up in IMROZ and MAIA (median of 59.7 months and 56.2 months, respectively). The reference provided in the EAG report for MAIA had a median follow-up of 28.0 months. This is due to a misleading referencing in the CS (3 different references for MAIA instead of the one with 56.2 months of follow-up). This is incorrect as the follow-up periods in IMROZ and MAIA used to estimate a proportion of patients with a subsequent treatment are very similar, with medians of 59.7 months and 56.2 months, respectively. However, the reference provided in the EAG report for MAIA indicates a median	The EAG report has been amended as advised.

account for differences in trial follow-up and the fact that all trials are not completed/all patients did not have a PFS event/all patients did not have the opportunity to initiate a subsequent line of treatment. However, IMROZ and MAIA had the same follow-up in that case.		follow-up of 28.0 months. This discrepancy is due to misleading referencing in the CS, which cites three different references for MAIA instead of the one with a 56.2-month follow-up only. MAIA: https://doi.org/10.1016/S1470-2045(21)00466-6	

Issue 11

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG Response</th></tr>
<tr>
<td>P70, Table 36
“Deliver exclusively oral chemotherapy” was used as a description for all codes.
HRG costs are correct but not</td>
<td>
<table>
<tr><th rowspan="3"></th><th colspan="3">Company</th><th colspan="2">EAG</th></tr>
<tr><th colspan="2">Cost per administration</th><th rowspan="2">Source: NHS Reference Costs 2022/23[48]</th><th rowspan="2">Cost per administration</th><th rowspan="2">Source: NHS Cost Collection 2023/24[57]</th></tr>
<tr><th>CS Table 66</th><th>Company model</th></tr>
<tr><td>IV - First dose</td><td>£486.10</td><td>£502.15</td><td>Total HRG: SB13Z – Deliver more complex parenteral chemotherapy at first attendance</td><td>£509</td><td>Total HRG: SB13Z – Deliver more complex parenteral chemotherapy at first attendance</td></tr>
</table>
</td>
<td>Incorrect description of each HRG code</td>
<td>The EAG report has been amended as advised.</td>
</tr>
</table>

the description of each HRG code.	**IV - Prolonged first dose**	£544.86	£562.84	Total HRG: SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£598	Total HRG: SB14Z – Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance		
	IV - Subsequent dose	£393.16	£406.14	Total HRG: SB15Z – Deliver subsequent elements of a chemotherapy cycle	£430	Total HRG: SB15Z – Deliver subsequent elements of a chemotherapy cycle		
	SC - First and subsequent doses	£411.99	£425.59	Total HRG: SB12Z – Deliver simple parenteral chemotherapy at first attendance	£394	Total HRG: SB12Z – Deliver simple parenteral chemotherapy at first attendance		
	Oral - First dose	£322.00	£332.62	Total HRG: SB11Z – Deliver exclusively oral chemotherapy	£283.00	Total HRG: SB11Z – Deliver exclusively oral chemotherapy		
	Oral - Subsequent dose	£0.00	£0.00	Assumption	£0.00	Assumption		

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
P70 "The company has also generated results using final OS DRd MAIA trial data (Scenario B). The EAG considers that as IMROZ trial becomes more mature a comparison of IsaVRd versus DVd using final MAIA trial data will be informative." DVd is not the same regimen as DRd. "V" is used for Velcade (bortezomib) whereas R is used for Revlimid (lenalidomide)	"The company has also generated results using final OS DRd MAIA trial data (Scenario B). The EAG considers that as IMROZ trial becomes more mature a comparison of IsaVRd versus DRd using final MAIA trial data will be informative."	Typographical error	This is a typographical error. The EAG report has been amended as advised.

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th><th></th></tr>
<tr><td>P34, Table 8</td><td>Median TTD from IMROZ clinical trial</td><td>[redacted]</td><td>The EAG report has been amended as advised.</td></tr>
<tr><td>P41, Table 12</td><td>HR IsaVRd vs Rd from ITC</td><td>[redacted]</td><td>The EAG report has been amended as advised.</td></tr>
<tr><td>P41, Table 13</td><td>HR IsaVRd vs Rd from ITC</td><td>[redacted]</td><td>The EAG report has been amended as advised.</td></tr>
<tr><td>P50, Table 19</td><td>HR IsaVRd vs Rd from ITC</td><td>
<table>
<tr><th rowspan="2">Time (years)</th><th colspan="4">HR (95% CI) for IsaVRd (gamma distribution) versus comparators</th></tr>
<tr><th>DRd</th><th>Rd</th><th>VMP</th><th>VCd</th></tr>
<tr><td>1</td><td>[redacted]</td><td>[redacted]</td><td>0.21 (0.15 to 0.29)</td><td>0.35 (0.25 to 0.47)</td></tr>
<tr><td>2</td><td>[redacted]</td><td>[redacted]</td><td>0.18 (0.13 to 0.26)</td><td>0.33 (0.24 to 0.45)</td></tr>
<tr><td>5</td><td>[redacted]</td><td>[redacted]</td><td>0.16 (0.11 to 0.26)</td><td>0.32 (0.21 to 0.48)</td></tr>
<tr><td>5.67*</td><td>[redacted]</td><td>[redacted]</td><td>0.16 (0.11 to 0.26)</td><td>0.32 (0.21 to 0.48)</td></tr>
<tr><td>10</td><td>[redacted]</td><td>[redacted]</td><td>0.15 (0.10 to 0.26)</td><td>0.31 (0.20 to 0.50)</td></tr>
</table>
</td><td>The EAG report has been amended as advised.</td></tr>
</table>

<table>
<tr><td></td><td></td><td>28</td><td>[redacted]</td><td>[redacted]</td><td>0.14 (0.08 to 0.27)</td><td>0.31 (0.18 to 0.52)</td><td></td></tr>
<tr><td>P50, Table 20</td><td>HR IsaVRd vs Rd from ITC</td><td colspan="5"><table>
<tr><th rowspan="2">Time (years)</th><th colspan="4">HR (95% CI) for IsaVRd (Gompertz distribution) versus comparators</th></tr>
<tr><th>DRd</th><th>Rd</th><th>VMP</th><th>VCd</th></tr>
<tr><td>1</td><td>[redacted]</td><td>[redacted]</td><td>0.66 (0.43 to 1.01)</td><td>0.51 (0.32 to 0.82)</td></tr>
<tr><td>2</td><td>[redacted]</td><td>[redacted]</td><td>0.56 (0.40 to 0.78)</td><td>0.47 (0.32 to 0.68)</td></tr>
<tr><td>5</td><td>[redacted]</td><td>[redacted]</td><td>0.34 (0.17 to 0.66)</td><td>0.36 (0.20 to 0.62)</td></tr>
<tr><td>5.67*</td><td>[redacted]</td><td>[redacted]</td><td>0.30 (0.13 to 0.67)</td><td>0.33 (0.17 to 0.65)</td></tr>
<tr><td>10</td><td>[redacted]</td><td>[redacted]</td><td>0.15 (0.03 to 0.79)</td><td>0.22 (0.06 to 0.94)</td></tr>
<tr><td>28</td><td>[redacted]</td><td>[redacted]</td><td>0.01 (0.00 to 1.94)</td><td>0.04 (0.00 to 5.32)</td></tr>
</table></td><td>The EAG report has been amended as advised.</td></tr>
</table>